ADVANCES IN INTERNAL MEDICINE

VOLUME V

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VOLUME I (out of print)

VOLUME II

VOLUME III

)LUME IV

ADVANCES *in* INTERNAL MEDICINE

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VOLUME V 1952

THE YEAR BOOK PUBLISHERS INC

For Great Britain and Northern Ireland
Interscience Publishers Inc
2 Southampton Row London, W C 1

PRINTED IN U.S.A

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Diseases of the Pregnant Woman Affecting the Offspring

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THE FACT that noxious influences affecting the developing ovum may result in definite changes in the embryo and thus give rise to abnormal offspring has long been known but it is only lately that the clinician has become aware of the importance of this subject The recent interest in this problem stems directly from Gregg s report in 1941 (54) of the detrimental effect of maternal rubella on the offspring As a result of his observations clinical medicine and teratology have become much more intimately associated This review will deal with the effect on the fetus of some of the more important illnesses affecting the pregnant woman but will not include syphilis erythroblastosis or the toxemias of pregnancy subjects which are dealt with in great detail elsewhere

Maternal disease may have the following effects on the offspring (*1*) it may leave the offspring unharmed (*2*) it may cause intrauterine death (*3*) it may result in premature birth (*4*) it may cause anomalies in fetal development It is particularly the last group the congenital malformations that have received greater attention during the past decade and their study has led to a much broader concept of their etiology and possible prevention (56 126) Developmental anomalies may be the result either of constitutional defects in the genes themselves or of adverse conditions affecting the developing embryo (145) The latter may be actinic dietetic or infectious Among the defects

due to disturbance in the germ plasm itself are the many hereditary diseases with which we are familiar In mice for example there are certain strains in which cleft palate regularly appears without any noxious influence affecting the mother (145) The subject becomes more complicated when one realizes that the very same abnormality may in one instance be due to an inherent defective germ plasm and in other instances can be produced by injury to the pregnant mother (146)

Teratology has been founded to a great extent on laboratory experiments and though results obtained in animal experimentation cannot always be applied to man many basic considerations are certainly applicable Some of the most fundamental work in this field was done by Stockard (127) who studied the results of physical and chemical injury of the developing egg by various environmental influences such as changes in temperature in the amount of oxygen it receives or the amount of water in its surroundings By such changes he was able to produce twins "double monsters or various single or combined malformations and he showed conclusively that the resulting anomalies were dependent on the stage of fetal development at which the injury took place (128) He speaks of "critical moments of origin for the organs of the embryo at which periods it is highly essential that the general developmental conditions and rate be at their optimum When we slow the rate of development we affect that part which chances to be developing at its maximum rate at that time while the more slowly developing parts are not so seriously injured if affected at all" (127) During the so called "critical moments the identical noxious influence may cause irreparable damage to the developing embryo whereas the same trauma operating during a "passive period" may have no effect at all He concludes that "The primary action of the treatments is to inhibit the rate of development and the type of deformity that results depends simply upon the developmental moment at which the interruption occurs"

These findings are extremely important for the clinician It is now common knowledge that illness of the pregnant woman during the first trimester when the embryonic development is most rapid is of more serious import for the offspring than if it occurs in the later months

The role of dietary deficiencies in the production of abnormal offspring is of extreme importance as shown by Warkany (144) who used the rat in his experiments and was able to produce certain defects

regularly For example when the mother s diet was deficient in vitamin A the fetus developed a fibrous retrolenticular membrane in place of the vitreous Other ocular defects were also produced When the same rats were given a diet including vitamin A the young were normal With deprivation of riboflavin certain skeletal defects appeared in the offspring and similar deprivation of vitamin D also caused specific fetal defects The importance of such experimental findings is obvious As Warkany states a better knowledge of the etiologic factors which lead to malformations will bring us nearer to the solution of the problem of prophylaxis"

The problem may also be studied from the epidemiologic view point, this has been done by Ingalls and associates (74 3 52 68) When large groups of defective infants are investigated it appears that in many cases maternal disease may be incriminated as a factor Syphilis toxoplasmosis and rubella are unquestionably harmful agents which result in fetal disease However the maternal illness need not necessarily be infectious it may be a local abnormality in the uterus itself causing disturbance in the blood supply of the developing embryo Disease of the placenta and faulty placentation may be potent factors On the other hand in a statistical survey of 677 congenitally defective infants born in the Boston Lying in Hospital 1930 through 1941 abnormal placentas were no more frequent than in a control group (126) The significance of antepartum bleeding is not thoroughly understood

That placental disease deprives the fetus of oxygen seems logical and in the mouse it has been shown that maternal anoxia may result in fetal death or in various congenital anomalies which vary with the degree of anoxia to which the mother is exposed and to the stage of gestation at which the experiment is performed Ingalls *et al* (72) who carried out these experiments advance the hypothesis that "rapidly differentiating tissues are more vulnerable to anoxia than resting or fully differentiated cells"

Maternal rubella (4) congenital tracheo esophageal fistula (75) encephalo-ophthalmic dysplasia (67 71) and mongolism (69 70 73) have been studied from the epidemiologic standpoint, with interesting conclusions That maternal rubella is the direct cause of a group of congenital defects is now well recognized and we find the expression "rubella syndrome" employed to describe the condition of the infant However there is no absolute unanimity of opinion that the other fetal defects just enumerated are due to disease of the mother The hypothe

sis that tracheo esophageal fistula depends on deleterious agents acting through the mother seems well founded This condition is now amenable to surgical cure and is therefore observed with more intense interest by the obstetrician and pediatrician since its early diagnosis is of great importance Ingalls and Pringle (75) have collected 107 cases of this rare anomaly and present considerable evidence that it is the result of maternal disease rather than of hereditary genetic factors There is only one report in the literature of 2 cases occurring in siblings These authors emphasize the frequency with which it is associated with other congenital defects so called synchronisms and on the basis of the morphology of the tracheo esophageal defect and that of associated arrests the syndrome is postulated as acquired during early fetal life—with departures from normal sequences of development occurring at about the fifth or sixth week These defects may occur through agents acting upon the placenta and the mother

Among the various types of abnormality of the newborn infant none is more important than mongolism with a frequency of occurrence stated by some to be as high as 3 of every 1 000 births (13) Many investigators now consider this condition to be due to noxious influences acting upon the mother with resulting disturbance of the developing fetus rather than to genetic factors Benda (13) who has studied the histories of about 400 cases of mongolism believes that "neither a germ mutation nor a primary inferiority of the ova is an acceptable explanation" In his opinion mongolism is due to a slowing of the developmental rate after the organogenetic period of gestation and that as a result the infant is an immature and "ill finished" individual Among the maternal symptoms which may contribute toward the fetal abnormality Benda lists advanced age of the mother a long period of inability to become pregnant impaired hormonal regulation bleedings during pregnancy menstrual irregularities previous abortions and uterine and ovarian anomalies "The common denominator is a threshold condition of sterility"

Ingalls has also collected a large amount of data on this deformity and has subjected previously reported cases to critical examination (69 70 73) He concludes (70) that though many different causes may be able to bring about mongolism "the causative mechanisms are few in number and operate at about the eighth week of fetal life Causative agents include uterine hemorrhage threatened abortion pathologic abnormalities of the uterus and certain intercurrent infections Experimental and clinical evidence suggests that lack of oxygen

to the fetus may be an important mechanism with temporary starvation and the accumulation of toxic metabolites to be evaluated"

The various types and frequency of appearance of synchronisms (i e defects of different organs occurring at the same time of gestation) such as cardiac defects irregularities in the osseous development of the hand especially the dwarfed middle phalanx of the fifth finger cataracts epicanthus brachycephaly and others strongly suggest injury to the developing embryo between the sixth and ninth weeks of fetal life

It is of special significance that a few cases have been reported in which women having rubella during the first trimester of pregnancy have given birth to mongolian idiots (73) To the 8 such instances in the literature (70) I can add the following case

B G the second child of healthy American parents was born at term after a normal labor The older child was healthy The mother was Rh positive During the sixth week of pregnancy the mother was exposed to rubella Several weeks later she became ill with what her physician called a virus infection He did not know of the exposure to rubella The mother could not recall having had an eruption She had never previously had rubella Except for this illness in the first trimester the pregnancy was entirely normal

The infant was mongoloid in appearance had a systolic precordial murmur and bilateral congenital glaucoma with some proptosis He grew up in an institution blind and severely retarded

Although rubella was not diagnosed during this mother s illness the exposure to rubella followed by what was termed "virus disease is most suggestive The combination of faulty development of the eye heart and brain are typical of damage by rubella

We have become so accustomed to regarding defective offspring as the result of genetic hereditary factors that when the physician encounters a congenital defect he often completely ignores the history of abnormalities in the present or in previous pregnancies The following cases are illustrative examples

Case I Baby L was admitted at age 3 days to the Pediatric Service of The Mount Sinai Hospital with symptoms of tracheo esophageal fistula The diagnosis was confirmed by roentgenograms and on operation The infant had convulsions before admission continued to have them postoperatively and died the day after operation At autopsy in addition to the tracheo esophageal fistula there was found the rare anomaly of a communication between the aorta and the pulmonary artery situated just above the aortic valves A small interventricular septa defect was also present

When a more detailed obstetric history was later obtained it was

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factors such as hormonal imbalance (diabetes) erythroblastosis or poisons such as lead In comparing his two groups of women he found that the mean age of the mothers with defective infants was significantly higher than that of mothers of normal offspring that there was a positive correlation between multiparity and fetal malformations that there was a history of previous abortions in 19 5 per cent of the abnormal group compared with 7 5 per cent in the normal and that ante partum hemorrhage occurred in 20 5 per cent of the former as compared with 4 3 per cent in the latter None of the mothers in this series gave a history of defects their general condition was excellent nutrition was good and there were no signs of vitamin deficiencies Landtman concludes that the relatively high incidence of various morbid states during pregnancy among mothers with deformed children has led to the assumption that these states may be involved in the pathogenesis of fetal malformations"

Most investigators have taken it for granted that the teratogenetic effect of any noxious agent is the result of direct action on the embryo Thus in the case of rubella we think of the virus attacking the embryo directly through an abnormal or perhaps even an intact placenta That the question is not always as simple as this has been emphasized by Gillman and coworkers in South Africa (50) They noted that many of the native women suffered from severe malnutrition and this was believed to be the cause of the high percentage of sterility abortions infant mortality and low birth weight They postulated that in these women the absorbing surface of the intestines was so damaged that "abnormal products" entered the circulation and that these by combining with plasma protein might impair nutrition and cause severe metabolic changes They therefore chose for their experiments the dye trypan blue which has the property of uniting with plasma albumin and injected this into pregnant rats As a result they obtained many deformed animals in the litters born to these rats Of 697 young in 118 litters 19 2 per cent presented macroscopic defects either immediately or soon after birth The malformations included spina bifida hydrocephalus tail defects eye defects and others The percentage of affected young depended on the time of injection Rats injected before conception as well as during pregnancy produced young of which 25 per cent were malformed When the injection was given on the sixth or seventh day of pregnancy 65 to 80 per cent of the animals produced defective young Since that is the time the placenta and membranes are forming these may have been involved The

that about 2 years before this pregnancy the mother had had a spontaneous abortion in the fourth month. Her first visit to the obstetrician for the most recent pregnancy was at 3 months gestation. She had missed one period 3 months earlier and then had had intermittent bleeding during the next 2 months. She continued to stain intermittently thereafter throughout her pregnancy.

Case 2. Baby M. F. came under my observation in March 1951 at the age of 2½ months. She is the third child of healthy American parents whose two older children, a boy aged 4 and a girl aged 3 years, are perfectly well. There is no familial history of congenital abnormalities. The mother's menses are regular, and a week after a period failed to appear the Aschheim Zondek reaction was positive. The baby was born exactly at term. She weighed only 4 lb. 7 oz. but did not look like a premature infant. At age 2½ months she weighed only 6 lb. 7 oz.; length was 17[illegible] in. and head measured 12½ in., as did the chest. The following anomalies were noted: widely open sutures of the skull, bilateral clubfoot, bilateral dislocation of the hips, a branchial cyst in the left cervical region, dislocation of the second phalanx on the proximal phalanx of the fifth finger of both hands. The bones of the lower extremities showed marked delay in development. The skull had the roentgenographic appearance of a lattice skull (Luckenschädel).

On inquiry it was found that there had been staining throughout the first 3 months of pregnancy and that the mother had had an attack of erythema nodosum during the fourth week of pregnancy. The obstetrician had noted that the placenta had a curious appearance, but it was not further examined.

The fact that the infant was a dwarf is also worthy of comment, for one can postulate that a defective placenta might prevent transmission to the embryo of substances necessary for its growth. Experimental work on the hen has recently shown that a growth factor may be transmitted through the egg to her progeny by varying the type of protein in her diet (30). It is impossible to evaluate as yet the effect of erythema nodosum in the fourth week of pregnancy, but from our experience with rubella it is not improbable that it may have been a factor in the causation of the fetal malformations.

An interesting series of observations have been reported by Landtman (84), who has made a detailed study of the histories of 73 mothers of deformed offspring and compared them with those of 200 mothers of normal children. Among the maternal factors he considered are (*1*) age and parity of the mother, (*2*) maternal infectious diseases, (*3*) nutritional condition of the mother, (*4*) mechanical factors, (*5*) roentgen and radium irradiation, and (*6*) various fetal environmental

being transmitted to the infant This disease is common in the East it usually occurs in young nursing infants whose mothers suffer from vitamin B deficiency Occasionally however the disease appears soon after birth (147) Also in the Orient rickets has been observed in newborn infants of women suffering from osteomalacia due to vitamin D deficient diets (125) Another example is infantile anemia resulting from deficiency of iron in the diet of the pregnant woman Particular stress should be laid on the protein iron calcium and vitamin content of the maternal diet to insure a healthy infant

PLACENTA

The question of placental permeability is obviously of great importance in the consideration of fetal disease In an excellent brief review of this subject Eastman (37) points out that whether a substance traverses the placental barrier depends on the following factors "1 the type of placenta concerned a circumstance which varies with the species of the animal 2 the stage of pregnancy 3 the molecular weight of the substance in question 4 the selective activity which the placenta appears to exhibit in relation to certain substances Simple substances of small molecular weight readily pass the human placental barrier by diffusion and by using radioactive tracers it has been possible to study many details of this process (62) For example Flexner and co workers (44 45) using radioactive sodium showed that as gestation proceeds the rate of transfer increases until just before term when it falls The rate of passage is fastest in those animals having the least number of layers of tissue separating the two circulations and there is a definite ratio between the amount of sodium transferred and the rate at which the fetus is growing (45)

By means of radioactive iron it has been shown that the fetus derives its iron not as was formerly believed from the iron of broken down maternal red cells but from the iron present in the maternal serum (3) Drugs such as penicillin (155) and streptomycin (156) when given to the mother appear rapidly in the amniotic fluid and the fetal blood (9 10) It is well known and of great practical importance that anesthetics and sedatives readily pass from the mother to the fetus That ether passes through the placenta and may be found in the blood of the newborn infant was shown by Smith and Barker (124) Morphine also traverses the placenta and this must be kept in mind where pregnancy is complicated by morphine addiction Interestingly enough

authors compare their results with the clinical findings in human rubella and go on to say In maternal rubella the period of greatest vulnerability of the human embryo coincides not only with a time when the embryo is actively differentiating its somites but also with the time when the chorion by means of its rapidly forming villi establishes intimate contact with the maternal blood and simultaneously attaches the embryo to the decidua Moreover the trypan blue apparently did not cross the placental barrier it could not be demonstrated in the tissues of the embryo and if it was present it was in a colorless form

These experiments are certainly provocative and suggest that at least in rats metabolic disturbance of the mother may have great effect on the developing fetus They also again emphasize the importance of the time when the injury to the pregnant mother takes place

MATERNAL NUTRITION

Severe deficiencies in the diet of the pregnant woman have a deleterious effect on the developing fetus Many important studies have been carried out on problems connected with maternal diets and one may safely say that with an optimum diet the human mother runs less chance of toxemia and that the occurrence of neonatal mortality still births and prematurity are reduced (21–23) During the period of severe food shortage in occupied Holland (1944–45) it was shown that there was a definite decrease in the weights of the newborn infants and also in their length (123) That a poor maternal diet not only affects the newborn infant but may influence its health during the first months of life was shown by experiments conducted by Ebbs *et al* (38) who studied the diets of 400 women in the low income group and supplemented their poor diets in the last 3 months of pregnancy

It is very tempting but incorrect to apply to man the results of animal experiments on diets in pregnancy Warkany's (146) experiments on the effect of vitamin deficient diets in rats have particularly stimulated great interest in the subject Other investigators have reported on various other aspects such as brain hemorrhages in the offspring of rats fed on synthetic diets deficient in vitamin K (19) By altering the type of protein fed to hens a growth factor could be transmitted through the egg to the young chick and in another set of experiments the cystine and methionine content of the egg could be altered (30) I an beriberi is an example of maternal vitamin deficiency

to blanch scarlet fever eruptions by means of placental serum thereby proving the presence of antibodies in the infant's serum

The transmission of immunity from mother to fetus has been used by Cohen and Scadron (28) to protect the newborn infant against pertussis by inoculating the pregnant mother with pertussis vaccine and in the same manner it has been possible to protect the newborn infant against tetanus by the injection of tetanus toxoid into the mother (85 137)

Bacteria may be directly transmitted from mother to fetus though here again there is no proof that the placenta is intact Syphilis is a case in point There are records of women suffering from gonorrhea who gave birth to infants with gonococcal polyarthritis (91) Congenital pneumonia as a cause of stillbirth is frequently encountered

Typhoid fever in the mother may cause fetal death with resulting abortion or premature labor The transmission of the typhoid bacillus through the placenta is a rare occurrence but has been proved to occur In an exhaustive review of this subject Lynch (90) comes to the following conclusions

1 The typhoid bacillus may pass from the mother to the child in utero
2 The resulting disease is a fetal septicemia
3 In cases of placental transmission there are generally placental lesions of a hemorrhagic type
4 The child dies either in utero or soon after birth There is *no evidence* that the fetus may survive the infection in utero
5 Placental transmission is not the rule in typhoid
6 The Widal is not always given with the fetal blood even though placental transmission be proven When present it cannot be determined whether the agglutinating substances result from the presence of the typhoid bacilli or whether they have filtered through the placenta from the *mother's* blood
7 The agglutinating substances may be transmitted through the milk of a typhoid mother to the nursling The reaction in the nursling's blood is but transient and is always weaker than that of the *mother's*

Illnesses of the mother due to protozoa may also be transmitted to the infant *in utero* and two of the more important toxoplasmosis and malaria will be discussed in greater detail

VIRAL INFECTIONS

It has long been known that viruses grow well on young proliferating tissue and it is therefore natural that the embryo is a particularly suitable culture medium The use of the embryonated hen's egg as a

the offspring of a morphine addict may also be afflicted with morphinism (107 139) At birth these infants appear to be healthy but during the first day they become restless and irritable and have attacks of sneezing and yawning Anorexia vomiting and diarrhea follow often with marked dehydration and weight loss Finally there are tremors coma and convulsions If the condition is recognized early and sedation administered promptly such infants may recover

It is well known that the human placenta is able to select certain substances and permit their passage to the fetus so that their concentration in the fetal blood exceeds considerably that in the mother's blood Vitamin C is a good example of such a substance the amounts found in blood taken from the umbilical vein may be several times greater than those in the maternal serum (89)

Complicated organic substances of large molecular size among them many types of antibodies are also able to cross the placental barrier Both the naturally acquired antibodies and those artificially stimulated in the mother may appear in the infant's blood As a result the newborn are immune during their early months of extrauterine life to those illnesses to which the mother has developed immunity Using Brucella abortus as antigen it has been demonstrated (17) that after active or passive immunization of the pregnant rabbit antibodies appear in the yolk sac showing that this structure is as permeable to foreign proteins as to those of maternal origin The routes by which immune substances reach the fetus or newborn organism differ widely in various animals In the ungulates (horse cattle pig goat sheep) antibodies are absent in the offspring at birth being transmitted through the colostrum and not through the placenta In these animals it is not until suckling takes place that antibodies pass into the blood of the newborn organism In man on the other hand the antibodies enter via the placenta and are present in the newborn though they may later be augmented by others transmitted through the colostrum (82)

Antitoxins bacteriolysins precipitins and complement fixing antibodies may thus traverse the human placenta Antibodies to influenza A (112) poliomyelitis (5) diphtheria (82) and other diseases have been found in the same concentration in both fetal and maternal blood Both the viral complement fixing and agglutination inhibiting antibodies to mumps (46) are transmitted from mother to child without any significant loss in titer In contrast titrations for streptococcus MG agglutinins show in at least half the tested cases a significant diminution of the maternal titer in the cord blood Toomey (134) was able

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hibiting fresh or healed lesions As a matter of fact we are not sure that even in rubella the virus is present in the developing fetus all we are certain of is that a fairly large percentage of cases of rubella occurring in the early months of pregnancy result in severe fetal damage

Pregnancy itself may alter the resistance of an animal to a viral infection Hodes (64) experiments with St Louis encephalitis virus showed that pregnant and virgin mice reacted quite differently to inoculation Though both were susceptible the former failed to acquire immunity until 7 weeks post partum after which they regained their ability to develop immunity Not only did pregnancy interfere with the acquisition of immunity but it diminished a previously acquired immunity

Another factor affecting the growth and propagation of virus in living tissue is the state of maturation of the tissue itself Thus Sabin and Olitsky (116 117) could cultivate the virus of vesicular stomatitis or of equine encephalomyelitis in the chick embryo but found the 4 day old chick completely resistant to them This change in susceptibility holds not only in comparing the embryo and the newborn animal but is also observed in comparisons of the young and adult animal (86) Viruses which invade the central nervous system such as equine encephalitis virus act quite differently in young and adult animals (115 116) When this virus is injected into the muscle of the young mouse it grows rapidly the older animal however cannot be infected by the intramuscular route As the animal grows older barriers form in certain of its tissues and the virus is halted at particular sites depending on the pathways it must travel Both the young and the old mouse may be infected with encephalitis virus by intracranial inoculation when the abdominal and intramuscular routes are used the end results are entirely different in the two age groups In 15 day old mice 100 per cent of the animals are susceptible at the age of 1 month only half of the mice are infected while only 5 per cent of 3 month old animals react In certain cases the resistance appears to be in the vascular system in others in the muscle or myoneural junction In an adult mouse resistant to infection by the intramuscular route the virus if injected directly into a nerve will result in an ascending fatal myelitis To quote Sabin (115) not all tissues in the same animal are necessarily equally susceptible to a given virus and when the virus must travel along distinct cellular and neuronal pathways such insusceptible zones can form a barrier to its further progression" Sabin also was able to show that the state of the animal s nutrition and its diet during

tissue culture for viruses is an example and mammalian embryos have been successfully infected with various viruses by laparotomy of the pregnant animal and direct inoculation of the fetus Pertinent and fascinating are the studies of Goodpasture (51) on the virus infection of the mammalian fetus His work was done before the discovery of the effect of rubella during pregnancy but he comments on the importance of prenatal viral infections as a cause of abortion An excellent example of this is the disease known as the virus abortion of mares in which the inoculated mare presents little or no evidence of disease but the foal becomes extensively infected resulting in death and abortion

Goodpasture grafted human skin on the chorioallantois of the chick embryo and attempted to inoculate it with varicella or herpes virus but failed with both He then used fetal cells i e the human amnion in place of the human skin and was able to cultivate the virus of herpes simplex variola and vaccinia He found that the resistance of various types of tissue to virus differed thus the virus of mare s abortion could be grown on grafts of amnion but not on chorion grafts The amnion seemed to be much more susceptible than the chorion a significant fact when one considers that in animals having the hemochorial type of placenta (rodents apes and man) the resistant chorion is in direct contact with the mother s blood These facts led Goodpasture to believe that virus infections in the fetus are probably due to lack of continuity in the tissues such as an infarct or an inflammatory area rather than that they traverse the intact placenta In support of this he quoted Markham and Hudson who said "the remarkable resistance of the chorionic epithelium to infection and injury when surrounded by masses of infected fetal mesenchyme is a striking feature of the placental pathology In one bacterial disease on the other hand Brucella abortus which may be transmitted in animals from mother to fetus the chorion seems to be particularly vulnerable and its cells may be seen densely packed with bacteria (17)

It has been shown in the case of the virus of vaccinia epidemic influenza and submaxillary gland disease of guinea pigs (24) that when an animal is susceptible the fetus is likely to be more so (48) In man however many viral diseases attacking the pregnant mother appear to leave the fetus unharmed (102) Influenza measles and variola may frequently cause the death of the fetus but viral diseases other than rubella are not commonly teratogenic It is definitely known that certain viruses pass from mother to fetus Variola will serve as an example a pregnant woman ill with the disease may give birth to an infant ex

malformation deafness microcephaly congenital glaucoma dental anomalies mental deficiency and other defects could be definitely traced to the mother s having had rubella during pregnancy The pains taking researches of Swan Tostevin and their collaborators (131–134) confirmed these observations and corroborated the fact that the mal formations occurred with greater frequency when the mother had ru bella during the first trimester of pregnancy At first it was believed that if the mother s illness fell within the first 6 weeks of pregnancy the fetus was defective in almost 100 per cent of the cases later it became apparent that the data had been obtained entirely from a study of groups of defective children A much lower figure is obtained when the question of fetal damage resulting from rubella in the first trimester is approached from the angle of the mother s pregnancy Anderson (3) who collected from the literature 44 cases of maternal rubella in the first trimester found 22 defective infants When the illness occurred in the second trimester 3 of 22 infants were affected and in the third trimester 2 of 14 Other Australian observers still believe that the inci dence of malformations is higher Dods (35) referring to Swan (131) set the chances of fetal damage as high as 75 per cent if the maternal illness occurs in the first 4 months A correct evaluation is very diffi cult to obtain (*1*) because the occurrence of mild rubella may be en tirely overlooked (2) because if the infant is normal the case is never reported and (3) because abortions are performed and the condition of the fetus remains unknown Careful obstetric histories with em phasis on maternal health and the subsequent outcome of the preg nancy if pursued in large obstetric services over many years in various parts of the world will finally answer this question At present we be lieve that if the infection occurs during the first trimester rubella causes congenital abnormalities in between 25 and 50 per cent of the pregnancies (99)

When the first Australian cases were reported the question was raised whether the disease was simple rubella or whether there might have been some other concomitant illness since there were many cases with severe sore throats and swollen joints (132 133) It was finally decided however that the mothers had had simple rubella I have seen cases of undoubted rubella in New York City in which the only sub jective symptom was a very sore throat with fever never higher than 100 F and in such uncomplicated rubella with an almost afebrile course definite swelling and tenderness of the small joints especially of the fingers were also present

That the occurrence of the "rubella syndrome in the newborn

the period of rapid growth greatly modified the appearance of these barriers to infection Data such as these show the complexity of viral infection in young rapidly growing tissues

Another interesting study of the effects of viral infection of the embryo is that by Hamburger and Habel (58) By inoculating the developing hen s egg with influenza A virus these investigators were able to produce a specific pattern of localized malformations In other words a group of unrelated defects in different organs which appeared regularly resulted from the virus inoculations They also experimented with mumps virus and obtained a different type of reaction They concluded their paper with the following paragraph

> Experimental evidence has been presented to show that influenza A virus (PR8) has teratogenetic effects on the early chick embryo It produces a specific syndrome comprising microcephaly and micrencephaly twist of the axis and impairment of growth of amnion Furthermore the virus is lethal for early embryos within three days after infection The mumps virus is also lethal for early embryos within five days after infection It does not produce specific abnormalities but seems to raise the incidence of malformations of the types which occur occasionally in uninfected chick embryos These results place influenza A virus in line with rubella virus as a teratogenetic agent Furthermore our observations on influenza A infections in chick embryos confirm the observations on rubella in humans in that only infections of early embryos result in abnormalities Chick embryos of four days incubation are killed by the influenza virus but it seems that at this stage of development most organs have passed the critical period at which their morphogenesis can be directed into atypical channels In this respect it is of interest to find that the patterns of infectiousness are different for the embryo and for the fully developed structures In the embryo the brain tissues seem to be particularly susceptible to influenza A virus whereas in the adult the respiratory mucous membranes are primarily affected In mumps the inflammation of the salivary glands is frequently combined with meningitis but no effect on the brain was found macroscopically in embryos The situation is the same as in rubella where the embryonic defects seem to have no obvious relations to the manifestations of rubella infections in older phases of life

RUBELLA

The announcement by the Australian ophthalmologist N McAllister Gregg (54) that there was a connection between the occurrence of an unusually large number of cataracts in the newborn and the presence of rubella infection in the pregnant mothers quickly spread over the medical world Surprise was expressed that a disease previously considered so mild should have such disastrous effects upon the human fetus Not only cataracts but as is now common knowledge cardiac

mality was the one most commonly encountered however various series show different types predominating

My own experience with the rubella syndrome includes 9 infants all but 1 of whom had ocular defects—7 with cataracts and 2 with glaucoma 6 were mentally retarded and 5 had cardiac disease

In Swan and Tostevin s (132) series of 37 infants with defects due to maternal rubella the abnormalities were found in the following order

ABNORMALITY	NO OF CASES
Deafness and mutism	26
Cardiac defects	19
Ocular defects	4
Microcephaly	2
Mongolism	1
Various other anomalies	6

In the cases collected by Patrick (106) the most frequently encountered abnormality was deafness then in order heart disease mental deficiency and cataract

In some institutions for the deaf in England the percentage of deafness due to rubella is very high (27) Of 18 deaf children in one school 8 gave a history of maternal rubella a ninth was probable and a tenth was possible In three other schools for deaf children 8 9 per cent of the inmates were born of mothers who had had rubella during pregnancy At the Lexington School for the Deaf in New York City with an enrollment of 262 there are at present 11 children with deafness due to rubella Altogether this institution has treated 16 such children 7 of whom had cardiac disease 3 had visual defects and 1 was mentally retarded

Carruthers (26) and Goodhill (50a) have pointed out that in this type of deafness the development of the organ of Corti is defective

Cardiac anomalies resulting from rubella belong to the noncyanotic group and are most frequently patent auricular or ventricular septal defects and persistent patent ductus arteriosus

Among the common ocular defects are cataracts which may be unilateral or bilateral and occur centrally in the lens glaucoma microphthalmos and buphthalmos

The rubella problem is enlightening since it is such an exquisite example of defects due to a postconceptional injury As previously mentioned before Gregg s discovery these defects would have been considered genetic in origin How delicate the mechanism initiating these changes in the developing embryo must be is well illustrated by

infant did not arise in Australia in 1940 has been shown by Beswick *et al* (14) who recently reported on twins born in 1930 and who had bilateral cataracts congenital cardiac defects deafness microphthalmia and mental retardation followed by epilepsy and glaucoma their mother had had rubella early in her pregnancy They also reported another postrubella syndrome which occurred in 1936 One of my own cases seen in New York City was due to rubella acquired in London in 1940 (9) Swan and collaborators in their later investigations also reported on children showing the rubella syndrome who had been born in 1938 and 1939 (131) Beswick and his collaborators attempt to explain why it is only a decade ago that the teratogenic effect of rubella was discovered They postulate that in Australia during the war many dwellers in rural areas were drawn into cities or camps and that when a large epidemic of rubella broke out it found many young susceptible adults and among them many pregnant women The natural result was an accumulation of congenital deformities The stage was set but it is greatly to Gregg s credit that he had the keen clinical sense to relate the cataracts to the previous occurrence of rubella In going back over the records of the Pediatric Department of the College of Medicine in Cincinnati Beswick could collect only 8 cases of infants with congenital malformations whose mothers gave a history of having had a rash during pregnancy 6 of them having a diagnosis of rubella two as measles Curiously enough none of these 8 had cataracts but all had other serious congenital defects These findings call attention to the need for obtaining a reliable history from the mother a most important point when one is faced with an infant showing a congenital anomaly

Rubella in the pregnant woman may result in abortion stillbirth a deformed infant or a normal child Wesselhoeft (148 149) has collected 31 cases that ended in abortion 27 occurring during the first 4 months of pregnancy I reported the case of a woman who had undoubted rubella in her sixth week of pregnancy followed by removal of a macerated fetus at 6 months She has had several normal children since then (7) I have also observed a woman in the sixth week of pregnancy who contracted rubella from her children and aborted spontaneously at the height of the disease

The defective infant is usually poorly nourished and underweight A single defect may be present though it is more common to find several defects Since the first publication was devoted to cataracts and other ocular defects the impression was gained that this abnor

was that not a single case of rubella occurred in the age group of 12 to 16 years Most of the cases developed in children between age 2 and 5 years Whether different strains of the rubella virus attack different age groups is not known but it is to be noted that in the 1940 epidemic in Australia and in England young adults particularly were affected

I have records of 9 pregnant women exposed to undoubted rubella 7 of them during the first trimester and 2 in the fourth month All 9 were given gamma globulin rubella did not develop in any An abortion was performed in 1 of the 9 another aborted spontaneously in the

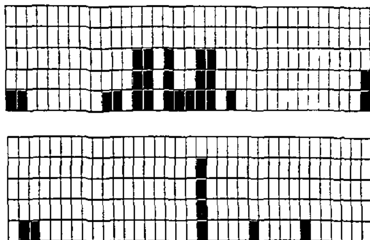


FIG 1—Comparison of occurrence of rubella in a child caring institution in (above) 129 controls who received no prophylaxis and (below) in 133 children given a prophylactic injection of gamma globulin (98a) Ordinates indicate number of cases abscissas indicate days after exposure and after injection respectively

seventh month (fetus not examined) and the remaining 7 had normal healthy infants The dose of globulin should be large 20 or 30 cc and should be given as soon as the history of exposure has been obtained There are no published records of large series of cases in which gamma globulin was used so definite knowledge on the subject is lacking In Australia however where the interest in the rubella problem is much greater than in America, a specific remedy has been made available by the production of gamma globulin obtained from the blood of rubella convalescents (92 99) To insure its specificity the blood is collected only from individuals stricken in epidemics in institutions or camps so that there can be no question that the donor had

the fact that several instances have now been reported in which the mother contracted the illness before conception with teratogenetic results Wesselhoeft (149) reported the case of a woman who had rubella 6 weeks before conception and gave birth to an infant with a congenital heart lesion bilateral cataracts and complete deaf mutism In another case reported by the same author a woman had rubella 10 days before conception and gave birth to an infant with patent ductus arteriosus bilateral cataracts and hydrocephalus That preconceptional rubella is not invariably harmful is shown by Swan and Tostevin (132) who reported on 2 mothers who had rubella 13 and 6 days before conception In the first the pregnancy was terminated and an incomplete examination of the fetus failed to reveal abnormalities in the second a normal infant was born There is 1 case recorded in which a woman in her second month of pregnancy was exposed to 2 children ill with rubella though she remained well her infant was born with cataracts and congenital heart disease (145) Rubella may be so mild that it altogether escapes the patient's notice As has been *proved experimentally by the inoculation of human volunteers (80)* the disease may run its entire course without the appearance of a rash

Once the pregnant mother shows evidence of rubella the physician is confronted with the decision whether or not to terminate the pregnancy A pregnant woman who has not previously had the disease should be given gamma globulin on exposure to rubella in the hope of preventing the illness There is no definite proof that gamma globulin derived from pooled blood can prevent the disease but there is some evidence in its favor and in the absence of any better product it should be given An epidemic of rubella among 262 children in a large child caring institution has been studied and an attempt made to determine the prophylactic value of gamma globulin (38a) A total of 133 exposed children were each given 6 cc of gamma globulin 129 children who were not given gamma globulin were used as controls Treated and control children were strictly alternated Figure 1 shows that rubella developed in 2 of the children given gamma globulin and in 2 of the controls within the first 2 days after the experiment was begun these cases were excluded as it was felt that they had been exposed too long before From the fourth through the thirty fifth day after injection rubella developed in 6 of the treated children and in 22 of the controls These results led us to believe that gamma globulin might have been effective in preventing rubella though it was not efficacious in every case One noteworthy finding in this experiment

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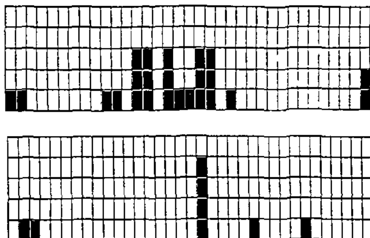


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If the disease is contracted after the fourth month of gestation the pregnancy should be permitted to proceed

No efforts should be made to prevent girls and young women from acquiring rubella since one attack usually confers lasting immunity In fact I believe they should be purposely exposed if the disease occurs in their families It has been shown by Australian workers (3 99) that throat washings obtained at the height of the disease contain the virus and rubella has been transmitted to susceptible volunteers by spraying the throat with this material The virus may be stored at −70 C and will remain active for at least 2 years Whether this material should be used regularly to produce the disease thereby causing immunity is questionable Since the washings may contain other viruses besides that of rubella and since recipients would have to be isolated the experimenters have been deterred from proposing general use of this procedure The fact that rubella may on occasion be complicated by serious encephalitis must not be forgotten

Since defective children have been born to mothers who had rubella before conception one should warn women of childbearing age not to become pregnant for several months after their illness Not only must susceptible pregnant women be cautioned to avoid contact with rubella but even women who have had the disease and consider themselves immune should avoid exposure This last precaution is advised by Schick (119) as a result of his recent findings in smallpox

Measles

That measles in the pregnant mother may be transmitted to the fetus has long been known Many cases are on record in which pregnancy has been interrupted by maternal measles and the presence of a measles eruption in the fetus has been repeatedly described Since in diagnosis measles and rubella are often confused and since it is known that the latter may result in fetal anomalies measles has naturally also been suspected of having a deleterious effect on the fetus However whereas rubella has a definitely harmful effect on the developing fetus the harmful effect of measles (morbilli) is questionable

Packer (103) has made a most comprehensive review of this question His results are based on a questionnaire sent to all married women reported as having measles during a large epidemic (11 000 cases) of the disease in Australia Packer was able to report on 18 women who had the disease during pregnancy There were no maternal deaths and

rubella The gamma globulin fraction of convalescent serum has been used in Australia for 2½ years and has been placed at the disposal of all practitioners In the last report on its use (92) it had been administered to 670 patients of whom 520 had been followed Rubella developed in only 7 of these women The group conducting these experiments is very cautious in its conclusions but believes as the result of its findings that if 4 cc of this globulin is given within 8 days of exposure the chance of preventing the disease is good In the 7 failures 3 aborted 1 had a stillbirth and 3 appear to have had normal infants Unfortunately convalescent rubella gamma globulin is not obtainable in the United States

When a decade ago the Australian observers postulated that if rubella attacked the pregnant woman during the first 2 months of pregnancy the fetus would be damaged in practically every case many felt that termination of the pregnancy was justifiable But religious scruples and legal complications make the decision very difficult Although it is now believed that only 25 to 50 per cent of the infants are affected many authorities still favor abortion Thus Swan (132) said in 1946 We consider that in the absence of prophylaxis therapeutic abortion is entirely justifiable in the case of any woman who suffers from German measles in the first four months of pregnancy" Eastman (37) too plainly stated that he considers abortion justifiable Wesselhoeft (149) made an ardent plea for a change in the law to allow the physician to terminate these pregnancies legally How difficult the situation becomes especially for the obstetrician was well discussed by Kelly (78) He pointed out that according to the law in Australia (this also applies to many states in the United States) no abortion is permitted by law except if the mothers life is in danger It is only by the most devious methods involving the services of the general practitioner and the psychiatrist that the obstetrician can feel justified in terminating a pregnancy Kelly is against interference except in special instances In this country there is great difference of opinion and though undoubtedly many abortions are performed there are some hospitals where this is strictly forbidden The whole question has been so widely publicized that the patient herself is quite aware of the dilemma in which she finds herself Many women cannot stand the mental strain of waiting 6 months with the continued apprehension of bearing a defective child Such women in my opinion suffer definite mental harm from this anxiety and in these cases with the consent of a psychiatrist and a consulting obstetrician an abortion is justified

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only one severe complication (pneumonia) 12 of the 18 pregnancies were unaffected by the disease In 4 cases the pregnancy terminated prematurely but this did not seem to depend on the stage of pregnancy in which the mother acquired the disease Both in this series and in an equally large series reported by Swan (134) the percentage of interrupted pregnancies is much smaller than in earlier reports Thus Nouvat (100) who collected 89 cases of measles in the pregnant woman in 1903 reported interruption of pregnancy in 60 per cent when the disease occurred in the first 6 months and in 80 per cent when it occurred in the last 3 months more than half the infants were born with the disease evident or in the incubation period Packer comments on the fact that the disease in the fetus is often at the same stage as in the mother Apparently the measles virus may traverse the placenta at any stage of pregnancy Ballantyne (quoted by Packer) reported a case in a 6 month stillborn fetus at the same stage as the mother s illness I have seen an infant born at full term to a woman at the height of her disease in whom measles developed at the age of 1 week obviously the infant had been infected *in utero* The series reported by Packer and by Swan do not bear out the theory that rubella being a mild disease only maims the infants whereas rubeola being a severe disease kills them Of Packer s 18 infants only 2 showed a fetal defect (1 mongoloid 1 partly deaf) 6 of his cases occurred in the organogenetic period (fourth to tenth week) and in 4 of these the infants were normal In Swan s series normal infants were born to 5 women who had measles during the fourth to tenth week of pregnancy Thus 9 women who had measles during the vulnerable period gave birth to normal offspring The birth of defective infants to women who had measles during the first four months of pregnancy has been reported in 6 cases A group of American investigators (1a) collected material by questionnaire and from the literature and found 4 defective infants of 13 born to women who had had measles during the first trimester of pregnancy In another 2 cases of defective infants the women were immune to the measles but had been exposed to it during the first month of pregnancy neither woman had become ill but 1 infant had a cleft palate and the other a cleft palate micrognathia and a rudimentary ear (58) It is known that the smallpox virus may affect the fetus *in utero* though the mother may be immune to it Possibly measles may act similarly While the cases just cited may be a coincidence the occurrence of defective infants combined with maternal measles or exposure to measles should be reported

The conclusion that measles is in no way comparable to rubella in its harmful effect on the fetus is justified More data must be collected before anything definite can be said about the exact effect of measles and the percentage of affected offspring Whether pregnancy should be terminated or not in cases of measles presents no problem since the number of reported cases is altogether too small to permit definite conclusions

Poliomyelitis

Poliomyelitis in the pregnant woman may result in the death of the fetus In 131 cases collected by Aycock and Ingalls (4) 33 resulted in the birth of a dead infant In 3 instances the infant was defective and in 3 in which the mother s illness occurred in the ninth month "the infant was reported to have suffered from poliomyelitis" There is no recorded case in which an infant has shown signs of the disease at birth and almost without exception opinions favor the theory that in the few cases of poliomyelitis in the neonatal period the disease has been contracted during labor Since the virus may be present in the mother s stools there is ample opportunity for the infant to acquire the disease during the process of birth Harmon and Hoyne (60) in reviewing this subject said that "pregnancy has little if any influence on the course of poliomyelitis in a paralyzed mother and conversely that in utero infection of the fetus occurs with rarity if at all These authors obtained the spinal cord of a fetus dead from asphyxia as the result of the mother s bulbar paralysis and inoculated it into monkeys the presence of the virus could not be demonstrated The reason the virus is not transmitted to the fetus is said to be due to its absence in the blood except in very rare instances

Undoubted cases of poliomyelitis in very young infants have been reported (6 15 65) but even the case reported by Baskin in which the infant showed symptoms at the age of 3½ days has been challenged since there is a possibility that the incubation period of poliomyelitis may be as short as 3 days (41)

Poliomyelitis of the mother then may result in fetal death but so far there is no absolute proof of intrauterine passage of the disease

Other Viral Infections

Some attempts have been made during the past decade to collect statistics concerning the effect on the offspring of other maternal viral

only one severe complication (pneumonia) 12 of the 18 pregnancies were unaffected by the disease In 4 cases the pregnancy terminated prematurely but this did not seem to depend on the stage of pregnancy in which the mother acquired the disease Both in this series and in an equally large series reported by Swan (134) the percentage of interrupted pregnancies is much smaller than in earlier reports Thus Nouvat (100) who collected 89 cases of measles in the pregnant woman in 1903 reported interruption of pregnancy in 60 per cent when the disease occurred in the first 6 months and in 80 per cent when it occurred in the last 3 months more than half the infants were born with the disease evident or in the incubation period Packer comments on the fact that the disease in the fetus is often at the same stage as in the mother Apparently the measles virus may traverse the placenta at any stage of pregnancy Ballantyne (quoted by Packer) reported a case in a 6 month stillborn fetus at the same stage as the mother s illness I have seen an infant born at full term to a woman at the height of her disease in whom measles developed at the age of 1 week obviously the infant had been infected *in utero* The series reported by Packer and by Swan do not bear out the theory that rubella being a mild disease only maims the infants whereas rubeola being a severe disease kills them Of Packer s 18 infants only 2 showed a fetal defect (1 mongoloid 1 partly deaf) 6 of his cases occurred in the "organogenetic period" (fourth to tenth week) and in 4 of these the infants were normal In Swan s series normal infants were born to 5 women who had measles during the fourth to tenth week of pregnancy Thus 9 women who had measles during the vulnerable period gave birth to normal offspring The birth of defective infants to women who had measles during the first four months of pregnancy has been reported in 6 cases A group of American investigators (1a) collected material by questionnaire and from the literature and found 4 defective infants of 13 born to women who had had measles during the first trimester of pregnancy In another 2 cases of defective infants the women were immune to the measles but had been exposed to it during the first month of pregnancy neither woman had become ill but 1 infant had a cleft palate and the other a cleft palate micrognathia and a rudimentary ear (58) It is known that the smallpox virus may affect the fetus *in utero* though the mother may be immune to it Possibly measles may act similarly While the cases just cited may be a coincidence the occurrence of defective infants combined with maternal measles or exposure to measles should be reported

quently as occurs with rubella The question of mumps is interesting in view of the work of Hamburger and Habel which showed that definite developmental defects arose when the hens egg was inoculated with mumps virus

The inclusion of acute hepatitis in the series reported from Sweden is significant in the light of the recent work carried out by Stokes and co workers (129) in Philadelphia They reported on 25 infants born jaundiced or in whom icterus developed within the first 2 months of life Although the mothers had not been ill when the incubation period was considered it seemed to point toward infection of the infant *in utero*

TABLE II
VIRAL DISEASE IN 354 MOTHERS OF DEFECTIVE CHILDREN (57)

MATERNAL INFECTION	NO OF CASES	NO ABORTED	NO MALFORMED INFANT	NO NORMAL INFANTS
Rubella	28	2	1	25
Measles	20	3	0	17
Chickenpox	12	1 twin	0	12
Mumps	34	1	5	28
Acute hepatitis	29	2	1	26
Poliomyelitis	38	11	2	25
Scarlet fever	13	0	0	13

By injecting the mother s blood and that of the infant into human volunteers in 1 case these workers were able to produce the disease Possibly the mother is a silent carrier of the hepatitis virus Whether the virus is that of serum hepatitis or of infectious hepatitis has not been determined but it is noteworthy that in a considerable number of the cases the fathers had had hepatitis in the army some years previously

Varicella in the mother is apparently only rarely followed by the birth of defective offspring despite the fact that it is one of the diseases which may attack the fetus *in utero* There are a number of reports of varicella developing in infants in the first few days of life when the mother was recovering from the disease (25 88)

Smallpox it has long been known can pass from mother to fetus In 50 to 60 per cent of the cases it may cause abortion Pock marked infants may be born of mothers who have had the disease during pregnancy and stillborn infants may show pustules in the active stage of the disease Schick (119) has called attention to the interesting fact that the fetus may acquire the disease *in utero* even if the mother is immune as a result of a previous infection He has collected 40 such cases and explains their occurrence on the basis of the mother s immu

diseases besides rubella but the numbers of cases are so few that it is difficult to draw any conclusions

Table I summarizes the reports of 26 cases collected by questionnaire by a committee of the American Academy of Pediatrics (1a). In 8 cases of maternal mumps there were 2 defective infants and 6 normal

TABLE I
INCIDENCE AND TYPES OF DEFECTS IN CHILDREN FOLLOWING MATERNAL INFECTION (OTHER THAN RUBELLA) IN FIRST FOUR MONTHS OF PREGNANCY (1a)

Maternal Infection	Infants		1st —Births		2d —Births		3d —Birth		4th —Birth	
	Total	With Defect	Total	With Defect	Total	With Defect	Total	With Defect	Total	With Defect
Measles	13	4	3	0	4	1 mental deficiency	4	1 heart lesion pyloric stenosis	2	1 each harelip genu valgum
Mumps	19	3	4	1 imperforate anus	1	0	5	1 hypospadias	9	1 corneal opacities
Chickenpox	4	1	1	0	1	1 cataracts	1	0	1	0
Infectious mononucleosis	5	3	2	1 heart lesions	1	1 cataracts heart lesion	2	1 heart lesion	0	0
Poliomyelitis	36	2	2	0	5	1 club foot	16	1 heart lesion	13	0

Month of pregnancy in which infection occurred

ones 6 cases of maternal varicella resulted in 1 defective and 5 normal infants 5 cases of maternal infectious mononucleosis resulted in 3 defective and 2 normal infants

Swan and Tostevin (132) report 3 cases of maternal mumps 1 of varicella and 2 of herpes zoster all 6 women bore defective infants An interesting study was published in 1948 by Gronvall and Selander (57) They reviewed the obstetric histories of 354 Swedish mothers of defective children (Table II) and found that viral disease had occurred in 5 per cent of these women during pregnancy This rate was about tenfold that found in a large series of women who had given birth to normal infants

The only conclusion that can be drawn from these various reports is that other viral diseases beside rubella may possibly have a teratogenetic effect on the developing embryo although not nearly as fre

the tuberculous nature of the lesions in the infant must be proved (2) a primary complex in the fetal liver is proof of the congenital nature of the tuberculous changes since it can arise only from tubercle bacilli in the blood of the umbilical vein (3) if there is no primary complex in the liver the infection is congenital only if (*a*) tuberculous changes are found in the fetus *in utero* or at birth or a few days after birth and (*b*) in a child who lives longer than a few days if extrauterine infection can be excluded with certainty the child being immediately separated from the mother and kept in an environment free from tubercle bacilli (29)

More recently Harris (61) and co-workers after reporting a case emphasized the difference between congenital and neonatal infection The former they defined as tuberculosis in which the infection occurs before birth by way of the blood stream or by aspiration or ingestion of infected amniotic fluid *in utero* Cases due to inhalation or ingestion of tuberculous material in the birth canal during labor they termed "tuberculosis neonatorum

Hughesdon (66) reported 4 cases in 1946 and Amick Alden and Sweet (1) reported 4 cases of congenital tuberculosis occurring in one hospital (Gallinger Hospital Washington D C) to which they added 124 collected from the literature The subject is of practical interest for the following reasons (*1*) Tuberculous infection in the pregnant woman may be transmitted to the fetus even when the disease is of the mildest type In many of the reported cases it is true the mother suffered from the miliary form of the disease or a severe pulmonary form but in others the mothers did not realize that they were ill Even in mild cases there may be transitory discharge of bacilli into the blood stream with resultant infection of the fetus (*2*) Whenever a woman known to have tuberculosis gives birth to an infant the latter must be closely watched Repeated roentgenograms of the chest and tuberculin testing are essential Congenital tuberculosis was until recently fatal but several cases are now on record of infants who were saved by the prompt use of streptomycin (1 87)

TOXOPLASMOSIS

Toxoplasmosis though rare is still of great interest It is an example of a disease resembling the abortion disease of mares in which the offspring is born congenitally infected with an illness transmitted by an apparently healthy mother The disease is caused by a protozoan

nity being cellular rather than humeral so that the rapid transfer of antibodies from mother to fetus is impossible This fact is known in countries where variola is prevalent women there know that though they themselves are immune they should avoid contact with small pox during pregnancy lest their unborn offspring become infected

In 1947 a few cases of smallpox occurred in New York City and as a result some 5 000 000 persons among them many pregnant women were vaccinated Studies of these showed that there were no more fetal defects among the progeny of these vaccinated women than among the unvaccinated It was concluded that smallpox vaccination during pregnancy did not increase the incidence of congenital defects still births abortions or infant deaths (12)

CONGENITAL TUBERCULOSIS

That tuberculosis in the pregnant mother may be transmitted to the fetus has been definitely established (114) This does not occur as commonly as one would expect with as widespread a disease as tuber culosis As long ago as 1861 Jacobi (75) referred to an infant born prematurely at 7 months who died a few minutes after birth and re vealed on postmortem examination numerous tubercles in the liver spleen and pulmonary pleura 3 weeks later the mother succumbed to tuberculosis This is a definitely proved case but not all the in stances reported in the literature are necessarily of true congenital origin The fetus may be infected through the blood stream or by inhalation or ingestion of infected amniotic fluid (104 152) It is how ever also possible that the infant acquires the disease while passing through an infected birth canal Before stating with absolute assur ance that the disease is congenital postnatal infection must be ex cluded The newborn infant is exceptionally susceptible to the tubercle bacillus even the briefest exposure to a tuberculous individual may be sufficient to infect the baby (33) Such a case was described by Bu chanan (20) an infant at the age of 2 days was held for 10 minutes in the arms of 2 children both of whom had tuberculosis The infant died at the age of 3 weeks and postmortem examination revealed mili ary pulmonary tuberculosis with caseous hilar glands the intestines were also involved but the liver was free from disease The infant therefore was most probably infected via the respiratory system

The most important work on the subject of congenital tuberculosis is that of Beitzke (11) He reviewed 100 cases and considered 61 of them as valid His criteria which have been widely quoted are (1)

MALARIA

That malaria in the pregnant woman may be transmitted to the newborn infant is known though whether the plasmodia enter the fetal circulation before labor or during the separation of the placenta is still in dispute (136) The evidence points toward infection during labor rather than during pregnancy In 1914 I reported a case of an infant born in New York City in December presenting splenomegaly a very severe anemia (hemoglobin 16 per cent) and great numbers of tertian parasites in the blood (8) The mother had had proved but untreated malaria in her fifth month of pregnancy To have acquired the disease through a mosquito in New York City in January or February seemed so unlikely that I was forced to conclude that the plasmodia were transmitted to the infant from the mother In the same paper was reported the case of a woman seized with chills and fever a few days before labor Plasmodia were found in her blood and in her infant s immediately after birth Numerous instances are on record in which the blood revealed plasmodia Another discussion of congenital malaria is that of D Antoni (32)

On the basis of published reports it must be concluded that malaria may develop in early infancy in the offspring of a woman who suffered from the disease during pregnancy

DIABETES

The subject of diabetes in the pregnant woman and its effects on the fetus is most intriguing Before the discovery of insulin pregnancy in the diabetic woman was extremely rare and when it did occur was attended with great danger to both mother and child Since the revolutionary change brought about by insulin therapy pregnancy in the diabetic woman has become frequent and many problems concerning the treatment of mother and child have arisen The great increase in fertility of the diabetic woman was well illustrated by Eastman (36) who wrote in 1946

> In 1909 J Whitridge Williams after thirteen years as head of the Obstetrical Service of the Johns Hopkins Hospital and despite a large consulting practice had himself encountered but one case of diabetes complicated by pregnancy During the past ten years in that same hospital among 227 married diabetic women between the ages of fifteen and forty five who were admitted sixty five or 28 6 per cent were pregnant By coincidence this number of pregnant diabetics seen at the Johns Hopkins Hospital during the

commonly found among rodents and birds How it is transmitted to man is not known Discovered first as a form of encephalitis in new born infants (153) it was later shown also to give rise to encephalitis in older children (114) and also as a fatal illness of adults resembling Rocky Mountain spotted fever with interstitial pneumonitis (108) In the newborn the disease is characterized by encephalomyelitis hydro cephalus chorioretinitis cerebral calcification and tendency to con vulsions Wolf *et al* (154) found the organisms in the infants tissues could transmit the disease to animals and discovered neutralizing anti bodies in the apparently healthy mother Toxoplasmosis in the neonatal period must be suspected in the presence of chorioretinitis in an infant with hydrocephalus or microcephalia this can be confirmed by roent genography of the skull which shows cerebral calcification (43) This congenital type of the disease with onset *in utero* often terminates fatally in the first few weeks of life or may remain asymptomatic until later in infancy It is important that in the mother the disease may be completely latent and asymptomatic the only proof of its existence being the presence of neutralizing antibodies in the blood

There are on record 8 instances in which a pseudocyst containing the toxoplasma has been found at autopsy in adults who had no known symptoms which might be related to these organisms (77) In all but 1 case the pseudocyst was in the heart A pregnant woman so infected may or may not give birth to an infected child In 2 instances toxo plasmosis has been reported in twins (42 157)

The absence of any major anomalies in the brains of affected infants suggests that the illness is probably acquired late in pregnancy In 1 case the infant also had situs inversus (29)

Of great interest is the fact that the birth of a healthy infant may follow that of an infant affected with the disease Sabin found a blood titer of 1 256 in the mother of an infant with toxoplasmosis the infant s titer was 1 1024 A sibling born 15 months later appeared to be per fectly healthy and showed at the age of 9 months a titer of 1 2 (141)

Eichenwald (39) who has demonstrated that in mice the disease may be transmitted through the breast milk suggested that "the fact that female mice can transmit the disease to their offspring *in utero* or through milk only while an active generalized infection is in prog ress rather than in the chronic carrier state may have some bearing on the observation that in a large majority of known cases in human infants one sibling alone was infected while the others showed no sign of present or past toxoplasmosis and gave negative serologic reactions

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It soon became evident that the mortality of offspring of diabetic women was high both in the intrauterine and extrauterine life that their body build was often abnormal and that they showed unusual symptoms shortly after delivery The incidence of abortion and sudden death *in utero* especially toward the end of pregnancy was found to be large (79) Hydramnios was a common complication and the occurrence of congenital anomalies was higher than in the infants of non diabetic women

The infants of diabetic women are known to be particularly large statistics show that from 15 to 25 per cent of these infants carried to term weigh over 10 lb whereas according to Eastman (35) the percentage of such overweight infants in the nondiabetic mothers is about 3 per cent A simple explanation would seem to be that this macrosomia is the result of maternal hyperglycemia but that such is not the case is now certain since well regulated diabetics whose blood glucose is controlled also tend to have oversized infants Finally observations made during the past decade have revealed the interesting fact that prediabetic women whose blood sugar is normal but who later become diabetic also tend to give birth to oversized infants Miller and Wilson (97) have shown that the infants of both diabetic and pre diabetic women present not only macrosomia but an enlargement of the heart even out of proportion to the weight and size of the large body This finding was demonstrated both by roentgenography and by a study of the heart weight at autopsy These babies are often edematous at birth and it is possible that the heart size and weight may at least in part be due to edema In Miller and Wilson s series of surviving infants the cardiac shadows gradually diminished in size so that after several months they were quite normal

Other pathologic changes that may be found in the fetus include increased glycogen content of the myocardium increased eosinophilia in the anterior portion of the pituitary hyperplasia of the adrenals gonads and islands of Langerhans and finally increase of erythropoietic tissue in various organs

Although the effect of isoagglutination of mother s and infant s blood and the question of erythroblastosis is not discussed in this review because it is not truly a disease of the mother one cannot discuss the pathologic findings in infants born of diabetic mothers without commenting on their extraordinary resemblance to those seen in infants

dying as the result of blood incompatibility As pointed out by Miller *et al* (96) about 50 per cent of the former show normoblastemia Edema hemorrhagic diathesis extramedullary erythropoiesis hyper plasia of the islands of Langerhans cardiac hypertrophy and early death are common to both conditions Both groups are more prone to congenital anomalies and both illnesses tend to be familial The groups differ in that the erythroblastotic child shows anemia and jaundice whereas these symptoms are as a rule absent in the infant of a diabetic mother The following case recently observed on the Pediatric Service of The Mount Sinai Hospital in New York City well illustrates this point

The infant a boy was admitted for erythroblastosis having been carried by the mother for 36 weeks The first child had been normal the second had required transfusion on the eleventh day of life the patient was the third child

The mother s blood was group A Rh negative the father s blood, group O Rh positive

The infant was icteric at birth with numerous purpuric skin lesions hemoglobin was 6 3 Gm red cells numbered 2 000 000 leukocytosis was present and platelet count was normal The response to the Coombs test was markedly positive Although an exchange transfusion was performed, the infant s condition rapidly grew worse and he died on the third hospital day Among the important pathologic findings was cardiomegaly the heart weighing 30 Gm (normal 17 Gm) with hypertrophied ventricles on section the muscle fibers were conspicuously vacuolated, with large deposits of glycogen The lungs were atelectatic The liver weighed 250 Gm (normal, 78 Gm.) and on section revealed areas of necrosis with hemorrhage and marked extramedullary hematopoiesis with atrophy of liver cells The pancreas showed great increase in the number of islands of Langerhans

The pathologic findings in this case of undoubted erythroblastosis fetalis are identical with those in infant fatalities due to maternal dia betes There was no history of glycosuria or diabetes in this mother

All investigators agree that the death rate of infants of diabetic women is higher than that of normal infants but statistics vary greatly and the figures have improved with newer methods of treatment Statistics published in 1944 (95) showed that the fetal and neonatal death rate was five times higher in the diabetic than in the nondiabetic pregnancies and that the mortality was just as high in infants born in the 5 years immediately preceding the onset of maternal disease These figures have been corroborated by Paton (105) Herzstein and Dolger (63) and others Even in mild diabetes where insulin is not required, the fetal and neonatal mortality is four times higher than in the non diabetic population

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number of cases in which determinations of sex hormones and 17 ketosteroids were obtained she found that in 64 cases in which there was no sex hormone imbalance fetal survival was 97 per cent there were no premature deliveries and there was only 1 case of toxemia On the other hand in 50 cases in which there was endocrine imbalance the fetal survival was 52 per cent pre eclampsia was present in 50 per cent and premature delivery in 40 per cent White also emphasizes the importance of vascular disease in the mother and shows how this factor grows in importance as the duration of the diabetic state lengthens The woman with diabetes of 5 years duration and therefore according to White in whom vascular disease has not yet had time to develop has just as good a chance to have a normal infant as the non diabetic woman However after 10 years of diabetes the risk of an abnormal pregnancy is infinitely greater Of women who have been diabetic for 20 years or more White states (151)

From our present data we believe that between 20 and 25 years duration of diabetes maternal survival fetal survival and maternal morbidity parallel the degree of pre pregnancy vascular disease that after 25 years of diabetes the fetal survival is hazardous the maternal morbidity probable and the maternal survival a gamble At the present time we are influenced to advise against pregnancy in diabetic women over thirty years of age whose diabetes is of 25 years duration

From the foregoing it is evident that there is no unanimity of opinion as to the etiology or the treatment of the symptoms which make their appearance in the neonatal period of the infant born of the diabetic woman There are as we have seen many factors militating against a favorable outcome These may be grouped as follows

(*1*) On the part of the mother they are (*a*) Duration of diabetic state (*b*) presence of vascular disease (*c*) obstetric abnormalities (uterine inertia uterine irritability hydramnion miscarriage) (*d*) toxemia (*e*) possible endocrine imbalance

(*2*) On the part of the infant they are (*a*) Large size (*b*) congenital anomalies (*c*) anoxia with resulting asphyxia (*d*) hypoglycemia (*e*) atelectasis

To obtain successful results in these cases meticulous care of the mother during pregnancy is of prime importance In this the obstetrician should be assisted by a clinician well versed in diabetic therapy Labor with delivery by cesarean section should be induced in the thirty sixth or thirty seventh week of pregnancy to avoid prenatal death (18) Whether the infant is premature or born at term whether

In 1936 Randall and Rynearson (110) reported 7 consecutive cases in which both mother and infant survived They stressed the delivery by cesarean section in the thirty sixth or thirty seventh week of pregnancy to forestall the sudden intrauterine death of the fetus a few days before term They advised administration of glucose to the newborn infant believing that hypoglycemia was the cause of its symptoms

An interesting series of 65 consecutive infants born to diabetic mothers in the clinic of Dr Elliott Joslin was reported by Sisson (121) in 1940 He called attention to the importance of anoxia in the newborn infant, with involvement of the nervous system manifesting itself in attacks of cyanosis twitching and extreme lethargy Of the 65 infants 57 per cent were normal and 43 per cent showed symptoms in the neonatal period The mortality was 18 per cent The cause of death in the 12 infants who died varied atelectasis was a frequent finding there were hemorrhages into various organs increased hematopoiesis and aspiration of amniotic fluid In only 1 infant was hyperplasia of the islands of Langerhans present The blood glucose concentrations during the first 12 hours of life were not particularly low and many infants who exhibited serious symptoms had normal blood glucose values Sisson stated that hypoglycemia in the newborn was rare and that when it occurred it might be due to the mother having received insulin a few hours before labor He stressed that although the infant s symptoms resembled those of hypoglycemia they might well be due to other causes especially cerebral anoxia In his opinion the routine administration of glucose to infants born to diabetic mothers was unnecessary

More recently Reis *et al* (111) published a study of a large series of cases (163 pregnancies of 52 diabetic women) Their over all salvage of viable babies was 86 4 per cent These authors come to quite different conclusions Their results differ from Sisson s in the blood sugar values They took blood glucose readings every 15 minutes during the first hour of life and found a much more rapid and a greater fall in blood glucose in these infants than in infants born of nondiabetic mothers They therefore routinely administer glucose to such infants even during the first 2 hours of life and say that "by overcoming anoxia lethargy and hypoglycemia which are the three greatest dangers to the new born child of the diabetic mother the overwhelming majority of these babies can and should be saved

White (150) who has had a particularly large experience in this field believes that endocrine disturbance of the pregnant diabetic woman is the most important etiologic factor In reporting a large

iron to offer her offspring who is then born with an insufficient supply of iron the result is hypochromic anemia after the fourth or fifth month of extrauterine life

Interesting experiments by Strauss (130) showed that the newborn infant s hemoglobin was not affected by maternal anemia However in the second half year of life anemia developed in children born of anemic mothers whereas in those born of normal mothers it did not The hemoglobin of infants of normal mothers averaged 67 per cent whereas that of infants born of anemic mothers averaged 46 per cent The infant therefore is able to draw even upon the anemic mother for enough iron for its immediate use but not enough to act as a store for future hematopoiesis

Maternal anemia is especially important in multiple pregnancies since the available iron is insufficient for two or more infants at one time The result is the frequent finding of anemia in twins or triplets

Hypochromic anemia of infancy usually responds quickly to oral iron therapy (10) Anemia in the pregnant woman may be avoided by proper diet by oral administration of iron and finally as proposed by Govan and Scott (53) and Slack and Wilkinson (122) by the intra venous injection of saccharated iron oxide

One type of anemia namely sickle cell anemia has a particularly harmful effect on the infant (31) Seife and Reich (120) reported 7 cases of pregnancy in women with sickle cell anemia and collected 38 additional cases from the literature These 45 women had 81 pregnan cies resulting in 11 spontaneous abortions 12 stillbirths and 8 ma ternal deaths Pregnancy appears to be harmful not only to the off spring but also to the mother The treatment consists in repeated transfusions

The possibility of the transmission of leukemia from mother to child is a frequently debated question There is no known case of a woman with leukemia giving birth to an infant suffering from the disease However leukemic women may become pregnant and bear normal children (55 81) There are also a fair number of cases of its occur rence as a familial disease (2 142) This is of particular interest since leukemia may occur in the neonatal period I observed a newborn infant who was thought to have a cephalhematoma which persisted for a number of days before it was discovered that the swelling was not a cephalhematoma but a leukemic infiltration The infant died within a few weeks with all the characteristic signs and symptoms of leukemia the mother showed no evidence of the disease Blackfan and Diamond

it is small or large and overweight it should receive the same treatment as given to premature infants The respiratory tract must be thoroughly suctioned The gastric contents should be aspirated immediately after birth since swallowed amniotic fluid may be regurgitated and aspirated causing asphyxia and possibly a so called hyaline membrane in the lung (49) The infant should be immediately placed in an incubator kept under constant observation and given oxygen If there is evidence of edema starvation for several days has been advised If twitching or other signs of possible hypoglycemia appear the blood glucose should be determined and glucose given by mouth or if necessary parenterally

Even with the best of care there is still an appreciable mortality in this group of infants As for the mother if her diabetes is not of very long standing and her case is properly handled the risk is not very great and Eastman goes so far as to say that "almost all maternal deaths to day from diabetes complicated by pregnancy are due to neglect

BLOOD DYSCRASIAS

Anemia of the pregnant woman has been known to be harmful to the offspring ever since Bunge in the last century postulated the theory that iron was deposited in the fetus especially during the latter part of pregnancy and that the newborn infant came to the world with a store of iron which had to last through a good part of his first year since during that period his food contained only very small amounts of this metal Until relatively recent years it was believed that the fetus received its iron from destroyed maternal red cells However by means of radioactive iron it has been demonstrated that iron is carried to the fetus not in the cells but in the maternal blood serum (143) Pommerenke *et al* (109) showed that radioactive iron given by mouth to the pregnant mother may be recovered from the fetus in as short a period as 40 minutes This is too short a time for the iron to have been incorporated in the mother s red cells then to be destroyed in the placental villi and finally carried over to the fetus to be absorbed into its red cells The iron received from the mother is not only used in the fetal red cells but is stored elsewhere in the fetal organism especially in the liver Moreover it has been shown (94) that the amount of iron stored by the fetus is in direct proportion to the amount of iron in the mother s diet The storage takes place especially during the second and third trimester of pregnancy If the mother suffers from anemia she has less

maternal rubella that focused attention on the subject and stimulated not only significant experimental studies but also awakened the pediatrician, the obstetrician and the internist to the importance of more careful observation of the pregnant woman Physicians immediately grew aware of the fact that an acute infectious disease in the pregnant woman could result not only in terminating the pregnancy or the birth of an infant malnourished or even suffering from the same disease as the mother but that it might result in definite congenital deformities Teratology which previously had been a science confined chiefly to the laboratory and the autopsy room suddenly became of vital interest, to the clinician

Though many congenital anomalies are due to defects in the genes and are truly hereditary in origin, we now know that some are certainly the result of diseases during pregnancy Although it is by no means possible to explain the occurrence of every anomaly or every fetal death yet a more searching inquiry into the history of the pregnancy may give a clue that may be helpful in clearing up the unknown cause The importance of the entire problem may be gathered from a conclusion of Stockard s that "defects in construction must be considered a disease which causes the death of about 23 per cent of the human race before or shortly after the time of birth" We are as yet able to account for the cause of only a small number of these deaths But emphasis on the postconceptional origin of fetal and infantile disease may help in solving some of the problems and as clinicians we should therefore be more keenly alert to conditions affecting the health and nutrition of the pregnant woman

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(16) reported only 2 cases of leukemia in the neonatal period among 200 cases in childhood

Thrombocytopenic purpura in the mother may result in definite disease of the infant The latest review (40) of this subject records 46 cases in which pregnancy was complicated by purpura and in these half the infants born alive had the disease at birth The total maternal mortality was 8 7 per cent that of the offspring 26 1 per cent Mothers with thrombocytopenic purpura may give birth to infants manifesting thrombopenia and all the signs of purpura at birth or in whom the symptoms develop shortly after birth Landolt (83) observed 2 cases and collected 19 reported cases He pointed out that in almost every case of infantile thrombocytopenic purpura the mother also has the disease Some of the mothers showed active bleeding during preg nancy others had only thrombopenia and may or may not have under gone splenectomy In some cases every child born to the woman may be affected by the disease Talmadge and Berman (135) reported the case of a woman who was splenectomized for thrombocytopenic pur pura at the age of 17 3 7 and 8 years later she gave birth to 3 infants All 3 infants exhibited marked thrombopenia petechiae and hemor rhages The petechiae appeared a few hours after birth the thrombo penia was extreme platelets being absent from the circulating blood The infants one of whom was followed for 5½ years all recovered and remained well The prognosis for the infants born alive in almost all the cases described was good There are a few recorded cases of normal women giving birth to children who showed all the signs of the disease immediately after birth (118) There are also reports of mothers suf fering from the disease whose children are entirely normal (93) and others in which one pregnancy has resulted in a diseased infant and another pregnancy in a normal child (140) It would seem that some mothers with thrombocytopenic purpura either transmit some ab normal substance or fail to transmit some necessary substance to their offspring resulting in temporary symptoms of the disease in the off spring Within a few weeks often without transfusions the infants are able to compensate for this disturbance and develop normally Whether there is a hereditary factor involved is not known nor do we know whether these apparently normal infants may later transmit the disease to the next generation

From the foregoing data one may conclude that the last decade has witnessed a remarkable increase in interest in maternal–fetal relation ship It was chiefly the discovery of the harmful effect on the fetus of

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Catheterization of the Heart*

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ONE OF the most significant developments in the field of clinical investigation has been the application of physiologic methods to clinical medicine Physiology has broken out of the laboratory and invaded the hospital ward This does not mean that the great advances physiology has made by means of animal experimentation have been of no value Rather experiments on animals performed during the last fifty years have become the basis for many diagnostic physiologic procedures on the human being A sharp demarcation between the diagnostic and the purely investigative studies cannot be made for they are intimately related However investigative studies as a rule precede those concerned with diagnosis Similarly a study of patients for diagnostic purposes will result in a better understanding of the disease processes

Catheterization of the heart permits circulatory studies in the human being which previously had been possible only on the anesthetized animal Catheterization has the added advantage over methods previously used with animals that it permits the study of circulatory phenomena in the intact human being without extensive physical trauma and without anesthesia

In the present report recent advances in catheterization of the heart and great vessels will be reviewed with particular emphasis on the developments of physiologic concepts which have arisen as a result of this technic

The author s original work summarized in this review was supported by grants from The Commonwealth Fund The Carolyn Rose Strauss Fund the Gulftex charitable foundation and the United States Public Health Service

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TECHNICAL CONSIDERATIONS

Recording of Pressures Through Catheter

A measuring instrument should reproduce and record the physiologic events in a true and undistorted manner and the recording system should have an adequate sensitivity and adequate frequency response Hansen (101) has shown that most of the existing manometers for determining the pressure in the body cavities containing air or liquid suffer from certain defects both clinically and physiologically This is the result particularly of the relationship between amplitude distortion phase distortion and the degree of damping

In general two systems for pressure recording are used The first is based on optical principles The optical manometer of Frank (83) is the prototype of these instruments A number of other workers (34 96 99 193) constructed similar apparatus Hamilton's (99) manometer is purely optical in contrast to most of the other manometers which use mechanical connecting parts The greatest advantage of Hamilton's optical system is that it permits attainment of a very high modulus of volume elasticity It is probably still the most accurate tool for the registration of pressures but its operation requires a certain amount of technical skill patience and knowledge In this respect however it does not differ from its electrical counterparts

The other systems used are based on purely electrical principles The movements of a manometer membrane are at once transformed into electrical energy which is then transferred to the ultimate recorder The transformation of the pressure impulse may be affected by (*1*) changes in electric resistance of a wire in proportion to its length (*2*) a piezo electric effect (*3*) induction phenomena and (*4*) changes in capacitance In the latter system an electric plate condenser is used in which the distance between the plates and thus the capacitance can be changed The excellent manometers of Lilly (131) and of Hansen (101) belong in this category The more frequently used commercially available pressure transducers are of the variable resistance type Because of their frequent use their properties will be dealt with in more detail

Dry cell batteries are sufficient to energize the transducers while the relatively large electric output of the transducer permits direct operation of many indicating and recording instruments Lambert and Jones (120) described in detail the properties of resistance wire man

HISTORICAL CONSIDERATIONS

Catheterization of the heart by the intravenous route was first performed in Germany by Forssmann (81), who was interested in the rapid injection of drugs into the heart However he noted that the method could have numerous applications in the field of metabolic and cardiovascular research The first catheterization was performed by Forssmann on himself In his first attempt Forssmann aided by another *physician introduced* 35 cm *of a no 4 ureteral catheter into an arm* vein Because as he writes his colleague considered continuation of the test too dangerous it was interrupted although "I felt perfectly fine" After a week Forssmann made another attempt alone This time he *was able to introduce the catheter into the right auricle and verified* the position of the catheter on a fluoroscopic screen "I observed the progress of the catheter in a mirror which was held by a nurse in front of the fluoroscopic screen Forssmann mentioned then that he had no untoward *sensation and that he considered the procedure safe There* is no doubt that his should be the credit for the first successful catheterization of the heart

Klein (117) working in Prague used catheterization of the right side of the heart for the first time to determine the cardiac output of man by means of the Fick principle Klein performed 18 catheterizations in 8 of which the heart was intubated in some instances the catheter also entered the inferior vena cava or the right ventricle Figures for cardiac output as determined by Klein ranged from 4 2 to 6 6 liters per minute The technic of Klein is almost identical with that used by most investigators at the present time and his should be the credit for the first physiologic application of the method

Injections of diodrast into the heart through a catheter were performed by Forssmann in 1931 (82) This procedure was also used by Egas Moniz *et al* (73) Heuser (108 Ravina (154) and Ameuille *et al* (1) In 1941 Cournand and Ranges (49) described the introduction of a radiopaque catheter into the right auricle of a human subject and standardized *the method for the determination of the cardiac out*put Since then a great number of investigators have used this method for diagnostic and physiologic studies both here and abroad An accurate determination of the pressures existing in the heart and great *vessels of man* by *means of the catheter was performed by Bloomfield* and co workers (22) and by Lenegre and Maurice (126) The recording of pressure curves is now indispensable to cardiac catheterization

TECHNICAL CONSIDERATIONS

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The other systems used are based on purely electrical principles The movements of a manometer membrane are at once transformed into electrical energy which is then transferred to the ultimate recorder The transformation of the pressure impulse may be affected by (*1*) changes in electric resistance of a wire in proportion to its length (*2*) a piezo electric effect (*3*) induction phenomena and (*4*) changes in capacitance In the latter system an electric plate condenser is used in which the distance between the plates and thus the capacitance can be changed The excellent manometers of Lilly (131) and of Hansen (101) belong in this category The more frequently used commercially available pressure transducers are of the variable resistance type Because of their frequent use their properties will be dealt with in more detail

Dry cell batteries are sufficient to energize the transducers while the relatively large electric output of the transducer permits direct operation of many indicating and recording instruments Lambert and Jones (120) described in detail the properties of resistance wire man

ometers They selected a gauge with relatively low sensitivity (Statham) They found the gauges to be linear and stable as long as a constant input was maintained Upon application of an approximately square wave pressure front the manometer indicated about 99 per cent of the pressure change within a fraction of a second Wiggers (192) by harmonic analysis and resynthesis of ventricular pressure curves demonstrated that the pressure pulse could be considered as composed of simple sine waves of different frequencies each with its own definite amplitude and phase relationship to the other sine wave components Accordingly in order to record accurately the pulse wave contours the manometer should be able to record sine wave pressure variations occurring at a frequency up to 20 cycles per second

Lambert and Jones found that the over all frequency response depends upon the response of each component part Factors influencing the frequency response are the volume elasticity of the manometer the internal diameter and length of the catheter and other connecting tubes the frequency response of the galvanometer and finally the specific gravity and viscosity of the fluid in the catheter The ideal means of recording pressures would be from a pressure pick up unit located at the tip of the catheter directly Such pressure pick ups based on a differential transformer have been built by Gauer and Gienapp (87) Recently *Ellis Gauer and Wood (75) applied such a system for the* recording of artefact free pressure tracings from the heart and great vessels of man and animals Their results indicate that the contour and magnitude of the central pulse can usually be recorded with a manometric system which possesses a uniform sensitivity of up to 5 cycles per second but only 32 per cent response at 60 cycles per second They believe that artefacts associated with motions of the catheter are primarily responsible for the poor intracardiac pressure tracings obtained with the conventional catheter manometer systems

The distorting influence of catheter movements on pressures recorded has also been stressed by Hansen According to this investigator the resiliency of the catheter plays a considerable part as the natural frequency *of the oscillating systems is only about one third that* of a rigid system of similar dimensions The main pressure distortions resulting from the use of a catheter are caused by the free damped vibrations occurring in the catheter They are started and maintained by the inevitable extrinsic influences to which the catheter is exposed during pressure determinations

General Technic

Adequate descriptions of the general technic of cardiac catheterization may be found in the literature (9 36 50 60 98 127 135 170 187 195)

Several types of catheters are in use The first type described by Cournand and Ranges (49) has one eye at the tip of the catheter (Fig 1) Goodale *et al* (89) described another type which in addition to this opening has two small eyes at each side and a groove connecting the side eyes with the eye at the tip (Fig 1) The author prefers the



Fig 1 —Two commonly used types of catheters The one with the side opening is the so called bird s eye catheter the side eye is connected to the end eye by a small groove

latter type because obstruction of the catheter by endothelial or endocardial tissue is less apt to occur on withdrawal of blood For the recording of terminal pressure when the catheter is pushed far out into the pulmonic or hepatic circulation and blocks the vessel completely the Cournand catheter should be used

The median basilic vein is usually employed for insertion of the catheter If this vein is too small the catheter may be introduced through the deep brachial vein This is particularly useful in small infants The great saphenous vein may also be employed particularly in very small infants It is usually difficult however to intubate the pulmonary artery by this route Catheterization may also be performed through the external jugular vein

In our experience general anesthesia has never been necessary In adults catheterization is performed without any premedication In children from 1 to 10 years of age a morphine–scopolamine mixture is

employed (Table I) Children under 1 year of age are given a rum water and sugar mixture through a nipple Fishman (80) has avoided venesection by using an expansile needle through which the venous catheter may be introduced Intra arterial catheterization is usually performed through either the radial or the ulnar artery Care should be taken not to introduce the catheter too deep into the ascending aorta because of the danger of intubating one of the coronary arteries However Lason *et al* (124) have successfully intubated the left ventricle in a series of patients by bending the catheter tip as it descends toward the aortic valve thus apparently avoiding the danger of catheterizing the coronary arteries Zimmerman *et al* (200) also reported catheter

TABLE I

MORPHINE SCOPOLAMINE DOSAGE

BODY WEIGHT KG	MORPHINE SULPHATE MG	SCOPOLAMINE MG
10	2 0	0 02
15	3 0	0 03
20	4 0	0 05
25	5 0	0 08
30	6 0	0 1
35	7 0	0 1
40	8 0	0 2
45	8 0 9 0	0 2
50 55	10 0	0 3
60 65	12 0	0 4
70 75	14 0	0 5
80 85	16 0	0 6

Morpl n do g ge e lly omput d o th b f 1 mg (1/64 g) pe 5 Kg of body w ight Scopol m d g d pe ds n th m rph ne d age b n e th two drug re alm t syn g l t s w to rr n th low s d

ization of the left ventricle in man The left ventricle was entered with no untoward results in 11 patients with syphilitic aortic insufficiency However 1 patient with rheumatic heart disease died of ventricular fibrillation Zimmerman (198) found an elevation of left ventricular diastolic pressure in patients in congestive heart failure This technic was used by Zimmerman and Hellerstein (199) for measuring intra cavity potentials of the human left ventricle Intra arterial catheteriza tions were also carried out by Farinas (78) Radner (153) Broden *et al* (33) and Jonsson *et al* (113)

It is important to move the catheter under fluoroscopic visualization only Otherwise the position of the catheter tip cannot be ascertained and serious errors in the diagnosis of intracardiac lesions will result The danger to patient and physician of repeated x ray exposure should

be kept in mind To avoid overexposure it is advisable to limit screening time to 5 minutes at 5 mill amperes The operator should wear a lead ap on and protect his hands by a lead shield or a lead apron placed under the arm and alongside the body of the patient Despite these precautions overexposure has been observed in physicians performing repeated catheterizations therefore routine observation of the differential blood count is vital

Blood is usually withdrawn through the catheter in 10 cc oiled and heparinized syringes after the catheter dead space has been washed out with a syringe Following the withdrawal of blood the saline drip through the catheter is restored Usually heparinized saline is used for the constant drip infusion through the catheter (15 mg of heparin per 1 000 cc of saline) Heparinization of the patient is unnecessary The oxygen content of the blood may be determined with the conventional Van Slyke method (185) or according to the method of Wood (195) This investigator has devised a photoelectric device which determines immediately the oxygen saturation of samples of blood withdrawn from the catheter

DANGERS DURING CATHETERIZATION

Complications which may be encountered are (*1*) venospasm (*2*) chills (*3*) acute attacks of anoxia particularly in pulmonic stenosis when the pulmonic artery is completely occluded by the catheter (*4*) cardiac arrythmias (*5*) venous thrombosis (*6*) air emboli

Venospasm may occur when there is difficulty in inserting the catheter into the vein or when the catheter cannot be introduced into the heart on the first attempt due to anatomic anomalies of the veins In my opinion the occurrence of venospasm does not reflect on the skill of the physician as has been suggested by Wood (196)

Chills are primarily due to pyrogenic substances probably remaining in the catheter from a previous test Chills may be avoided by thoroughly rinsing the catheter with sterile water followed by rinsing with a detergent solution The catheter should be boiled for ½ hour immediately preceding the catheterization I have found it useful to insert a stylet through the catheter with its tip reaching within 1½ inches of the catheter tip (Fig 2) This makes the catheter more rigid and places the lever point directly at the bend of the catheter

Acute attacks of anoxia due to occlusion of the pulmonary artery were observed in my laboratory in 2 cases of isolated valvular pulmonic

stenosis The attacks resulted probably from a sudden decrease in the cardiac output following occlusion of the pulmonary artery The resulting fall in cerebral blood flow probably initiated the attacks

Cardiac arrythmias are frequently encountered when the catheter enters the right ventricle or when it is pushed toward the pulmonary artery Goldman *et al* (88) Zimdahl (197) and others have performed extensive electrocardiographic observations during cardiac catheterization In the Goldman (88) series of 50 consecutive patients one or more types of cardiac arrhythmia developed during catheterization in

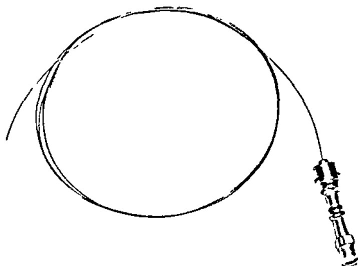


FIG 2 —Stylet to be introduced into the catheter

all but 1 In 60 per cent of these patients auricular premature systole developed Nodal premature systole was seen in 78 per cent Superventricular tachycardia of auricular or nodal origin occurred in 28 per cent and auricular flutter in 6 per cent In 85 per cent there was ventricular premature systole and in 78 per cent short bursts of ventricular tachycardia developed Ventricular flutter was seen in 6 per cent One patient had ventricular fibrillation during cardiac catheterization with a fatal outcome Southworth *et al* (174) describe recovery from ventricular fibrillation in a patient in whom the attack had been precipitated by cardiac catheterization Various degrees of auriculoventricular blocks were also not rare in the Goldman series and transient right bundle branch block developed in 12 per cent Bundle branch block is

not considered sufficient reason for discontinuing the catheterization. Particularly noteworthy is the fact that in all cases except the one with ventricular tachycardia withdrawal of the catheter resulted in cessation of the arrhythmias encountered. Prompt recognition of the appearance of these arrhythmias is therefore of the greatest importance and can be accomplished by continuous electrocardiographic observation during cardiac catheterization.

Bruce *et al.* (35) described a case of multifocal paroxysmal ventricular tachycardia occurring during cardiac catheterization in a patient with a probable Wolff Parkinson White syndrome. The ventricular tachycardia changed to supraventricular tachycardia after intravenous injection of atropine sulfate. I have studied the effect of procaine amide (pronestyl)* on the production of ventricular premature beats and on ventricular tachycardia. In approximately 50 patients the drug did not prevent the appearance of these arrhythmias during catheterization. I have no personal experience with quinidine but feel that the possible dangers of quinidine forbid its prophylactic use in catheterization of the heart.

Venous thrombosis is not frequent following cardiac catheterization. I have observed it in about 0.5 per cent of all catheterizations. In no case, however, has the thrombosis been progressive.

Air emboli have been personally observed in 4 of some 1,800 catheterizations. The neurologic symptoms were primarily of pontile origin but all symptoms disappeared after a period of hours without residual damage.

Venous catheterization of the heart, therefore, is a safe procedure provided certain precautions are observed. These include continuous electrocardiographic observation during catheterization, strict asepsis, and particularly thorough training and experience of the investigator. The period in which the catheter tip remains in the ventricle should be limited to 3 minutes or less. In patients with the cyanotic type of congenital heart disease *the arterial oxygen saturation may be well below* 70 per cent and in them all precautions must be rigidly enforced.

It is unlikely that catheterization of the human heart damages the endocardium. In dogs, however, endocardial lesions have been described following repeated catheterization. Ellis *et al.* (74) at the Mayo Clinic found endocardial damage consisting of mural thromboses or small myocardial necroses in 9 of 16 animals. Banfield *et al.* (4) also described endocardial changes in dogs following catheterization of the

* Squibb & Sons

heart I have examined the hearts of patients who have died of causes other than catheterization but who had undergone catheterization studies no pathologic lesions were found at autopsy One is justified in concluding that in man catheterization results in no detectable pathologic lesions of the heart

CATHETERIZATION IN CONGENITAL HEART DISEASE

Catheterization of the heart is of particular importance in the diagnosis of congenital heart disease Unquestionably the greatest diagnostic application of this technic may be expected in this field It seems advisable to stress here a number of points

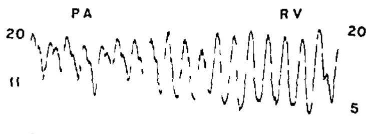


Fig 3—Tracings obtained from pulmonary artery (P A) and right ventricle (R V) of a normal individual Pulmonary artery systolic pressure is identical with right ventricular systolic pressure

(*1*) The catheter should be moved only under fluoroscopic guidance

(*2*) Pressures should be recorded from the chambers of the heart and great vessels *The normal blood pressure in the right auricle is plus or minus* 5 mm Hg in the right ventricle 25/0 mm and in the pulmonary artery about 25/10 mm (Fig 3) Deviations of pressures indicate hemodynamic disturbances caused by congenital or acquired heart disease For example in tricuspid atresia the second peak of the tracing usually representing the opening of the tricuspid valve is higher than the peak resulting from auricular contraction (Fig 4) In constrictive pericarditis a typical M shaped auricular tracing is observed The ventricular tracing shows the dip and plateau type of tracing which is characteristic of this disease (Fig 5)

(*3*) The oxygen content of blood in the various chambers of the heart the *superior and inferior venae cavae and if possible the pul*monary artery or the aorta should be determined Normally venous

blood from the vena cava does not mix well until it has reached the right ventricle Nevertheless there is normally little difference in the oxygen content of the blood in the superior vena cava right auricle right ventricle and pulmonary artery If the defect is between the auricles the oxygen content in right auricular blood may be signifi



Fig 4 —Right auricular pressure in tricuspid insufficiency Second peak of pressure tracing is elevated because ventricular contraction is transmitted into right auricle

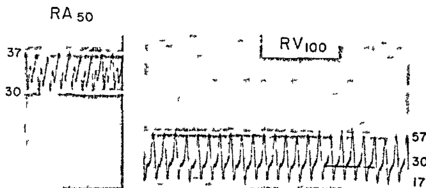


Fig 5 —Constrictive pericarditis Auricular tracing is M shaped ventricular tracing is of the dip and plateau type characteristic of this disease

cantly higher than the oxygen content of blood in the superior vena cava In a ventricular septal defect the oxygen content of right ventricular blood is higher than that of right auricular blood In the presence of a patent ductus arteriosus the oxygen content of pulmonary arterial blood will exceed that of right ventricular blood

(4) The volume of blood flowing through the various portions of the circulatory tree and the intracardiac and extracardiac shunts may be calculated from the oxygen contents of the various samples and the

oxygen consumption per minute determined by the usual technic for measuring basal metabolic rate The volume of blood flowing through the lungs and through the intracardiac or ductus arteriosus shunt is calculated from the oxygen contents of the blood samples and the oxygen uptake in the lungs

Formulas to accomplish this have been published from various laboratories (50 60) It should be emphasized however that most of the volume flows calculated with these formulas are approximations only Direct catheterization of the pulmonary vein in patients with auricular septal defects has shown a saturation of pulmonary vein blood of 96 per cent (85) For this reason the oxygen content of pulmonary vein blood was calculated from the oxygen capacity and on oxygen saturation of 96 per cent

Mixed venous blood is usually obtained from the pulmonary artery except in the presence of a left to right shunt in which case blood from the chamber or vessels immediately proximal to the site of the shunt is assumed to be representative of mixed venous blood

The formulas used by the author follow (17)

Systemic flow (ml /min) =

$$\frac{\text{0 uptake (ml /min)} \times 100}{\text{0 content of peripheral arterial blood (vol \%)} - \text{0 content of mixed venous blood (vol \%)}}$$

Pulmonary artery flow (ml /min) =

$$\frac{\text{0 uptake (ml /min)} \times 100}{\text{0 content of pulmonary vein blood (vol \%)} - \text{0 content of pulmonary artery blood (vol \%)}}$$

Effective pulmonary flow (ml /min) =

$$\frac{\text{0 uptake (ml /min)} \times 100}{\text{0 content of pulmonary vein blood (vol \%)} - \text{0 content of mixed venous blood (vol \%)}}$$

Over all shunt (left to right) = pulmonary artery flow — systemic flow
Over all shunt (right to left) = systemic flow — pulmonary artery flow
Total left to right shunt = pulmonary capillary flow — effective pulmonary flow
Total right to left shunt = systemic flow — effective pulmonary flow

Of special significance is the estimation of the effective pulmonary blood flow It represents the volume flow of blood which after its re turn to the right auricle ultimately reaches the pulmonary capillaries It has been called the effective pulmonary blood flow since it represents that component of mixed venous blood which becomes effectively

oxygenated in the lung (17) In the absence of a pathologic shunt no oxygenated blood reaches the pulmonary artery and no venous blood reaches the aorta so that the effective pulmonary blood flow equals the pulmonary artery and the systemic flows

Calculations have shown that in congenital malformations of the heart in which a septal defect is present the volume flow through the shunt is predominately unidirectional The only exceptions are complete and partial transposition of the great vessels In these malformations the unidirectional shunt is incompatible with life since it would lead either to depletion or hypervolemia of either the pulmonary or the systemic circulation (9 41) The over all intracardiac shunt represents the difference between the systemic and the pulmonary artery flow If the systemic flow exceeds the pulmonary artery flow the shunt is directed from right to left If on the other hand the pulmonary artery flow exceeds the systemic flow the intracardiac shunt is directed from left to right It should be borne in mind that in most instances there is reciprocal admixture through the defect The actual volume of the left to right current is represented by the difference between the pulmonary artery flow and the effective flow (total left to right shunt) Conversely the volume of right to left mixing currents is represented by the difference between the systemic flow and the effective pulmonary blood flow (total right to left shunt) In the presence of right to left admixture of blood the volume of total mixed venous blood which courses through the lung is decreased This will result in a fall in the ratio of effective pulmonary flow over systemic flow with a subsequent decrease in the peripheral arterial oxygen saturation Arterial oxygen saturation is not the result of decreased pulmonary blood flow but rather is due to a decrease in the ratio of effective pulmonary blood flow over systematic flow or expressed more simply is due to the right to left shunt The decrease in pulmonary blood flow reduces this ratio Reduction of pulmonary blood flow alone for example in isolated pulmonic stenosis does not result in arterial oxygen unsaturation

Catheterization of the heart in congenital heart disease has by no means eliminated the need for thorough physical examination or for the performance of other physiologic tests (exercise test oximetry measurements of the pulmonary capillary flow) The purpose of catheterization and of other physiologic studies in patients with congenital heart disease is primarily diagnostic Catheterization of the heart and related tests however also contribute to the understanding of disturbances in the internal environment (i e adaptation to chronic anoxemia)

oxygen consumption per minute determined by the usual technic for measuring basal metabolic rate The volume of blood flowing through the lungs and through the intracardiac or ductus arteriosus shunt is calculated from the oxygen contents of the blood samples and the oxygen uptake in the lungs

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between right auricular and right ventricular oxygen content may also rise The collateral circulation to the lung which includes the artificial ductus increases

The right ventricular systolic pressure is elevated There is a gradient between the pressure in the right ventricle and that in the pulmonary artery (Fig 7) There may be a pressure gradient from the

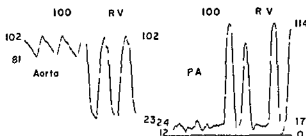


Fig 7 —Tetralogy of Fallot Pressure tracing obtained when catheter was pulled back from aorta into right ventricle (R V) through a high ventricular septal defect (left) and when tip of catheter was withdrawn from pulmonary artery (P A) through a pulmonic stenosis into right ventricle (right)

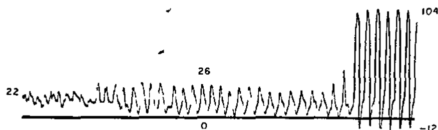


Fig 8 —Tetralogy of Fallot Pressure tracing obtained on withdrawal of catheter from pulmonary artery through pulmonic stenosis and through infundibular chamber into right ventricle showing existence of a pressure gradient between pulmonary artery infundibular chamber and right ventricle

pulmonary artery to the infundibular chamber and another gradient from there to the right ventricle (Fig 8)

Pseudotruncus Ateriosus In this condition the physiologic findings are similar to those observed in the tetralogy of Fallot (Fig 9) Pulmonary atresia cannot be recognized by cardiac catheterization Various types of truncus arteriosus have been described by Soulie *et al* (172)

Tricuspid Atresia with Defective Development of Right Ventricle The findings obtained by catheterization are illustrated in Fig

It is impossible in this review to describe catheterization findings in all congenital malformations of the heart The reader is here referred to the reviews of a number of investigators (9 36 50 72 98 110 127 170 195 196)

Following the physiologic classification outlined elsewhere (9) congenital malformations of the heart will be classified here in the following groups (*1*) pulmonary flow less than systemic flow and pulmonary artery pressure usually decreased (*2*) pulmonary blood flow greater

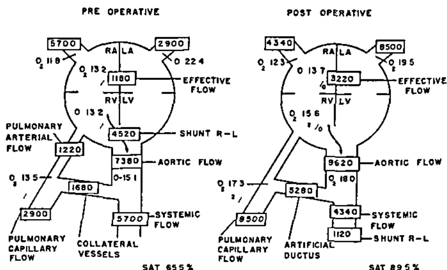


FIG 6—Tetralogy of Fallot Pre and postoperative circulatory findings

than systemic flow and/or pulmonary artery pressure normal or increased (*3*) pulmonary flow equal to systemic flow at rest and after exercise

PULMONARY FLOW LESS THAN SYSTEMIC FLOW PULMONARY ARTERY PRESSURE USUALLY DECREASED

TETRALOGY OF FALLOT This malformation consists of pulmonary stenosis or atresia with right ventricular hypertrophy interventricular septal defect and overriding of the aorta Figure 6 illustrates the circulatory findings in this condition The pulmonary flow is below normal and systemic flow shows marked variations The over all shunt is from right to left but there may be some total left to right admixture Postoperatively the total pulmonary blood flow increases and the gradient

between right auricular and right ventricular oxygen content may also rise The collateral circulation to the lung which includes the artificial ductus increases

The right ventricular systolic pressure is elevated There is a gradient between the pressure in the right ventricle and that in the pulmonary artery (Fig 7) There may be a pressure gradient from the

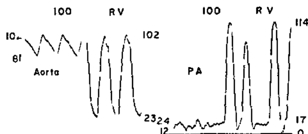


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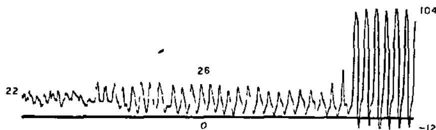


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Tricuspid Atresia with Defective Development of Right Ventricle The findings obtained by catheterization are illustrated in Fig

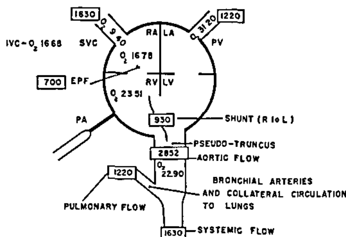


Fig 9—Pseudotruncus arteriosus Circulatory findings

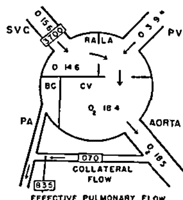


Fig 10—Tricuspid atresia Circulatory findings

ure 10 Catheterization may offer valuable information and greatly aid in the diagnosis (9 23) However if catheterization is to be of value the possibility of the diagnosis must be entertained and the procedure performed with this possibility in mind The diagnosis of tricuspid atresia should be suspected if the catheter enters a high pressure area from which blood of relatively high oxygen content is obtained On

withdrawing to the right atrium the catheter tip should pass to a low pressure area containing blood of a corresponding high oxygen content Figure 10 shows that in this malformation the systemic flow is usually

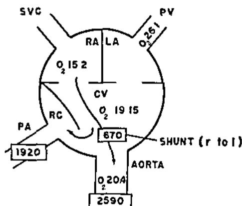


FIG 11 —Single ventricle with pulmonary artery arising from rudimentary outlet chamber Circulatory findings

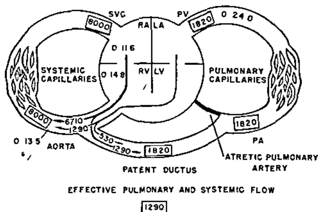


FIG 12 —Transposition of great vessels with atresia of pulmonary artery Circulatory findings

elevated The pulmonary blood flow calculated on the assumption that the pulmonary arterial oxygen content is the same as that of the right ventricle is decreased The effective pulmonary artery flow is also reduced The pressure in the common ventricles is elevated (23)

SINGLE VENTRICLE WITH PULMONARY ARTERY ARISING FROM RUDI

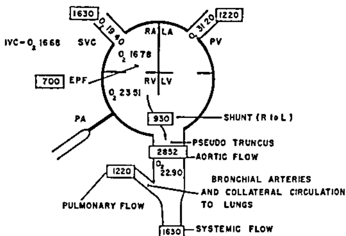
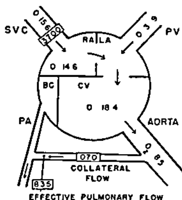


Fig 9 —Pseudotruncus arteriosus Circulatory findings



* CALCULATED
BC BLIND CHAMBER
CV COMMON VENTRICLE

Fig 10 —Tricuspid atresia Circulatory findings

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seen The right auricular pressure in patients with this malformation is usually increased

EBSTEIN'S DISEASE WITH PATENT FORAMEN OVALE This condition consists of downward displacement of the tricuspid valve usually ac

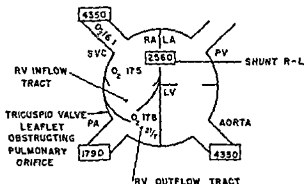


FIG 14 —Ebstein's disease Circulatory findings

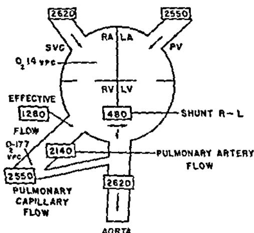


FIG 15 —Eisenmenger's complex Circulatory findings

companied by hypoplasia of the right ventricular muscle Figure 14 shows that there is a reduction in pulmonary arterial flow and an over all shunt from right to left The arterial oxygen saturation is decreased the pressure in the right ventricle is normal The low right ventricular pressure in most patients with Ebstein's disease is probably caused by the hypoplasia of the right ventricular muscle (9)

MENTARY OUTLET CHAMBER Usually the catheter does not enter the pulmonary artery or the rudimentary outlet chamber There is a difference in oxygen content between right auricular blood and blood in the high pressure chamber of more than 3 5 volumes per cent The over all shunt is from right to left (Fig 11) The differentiation between tricuspid atresia and this malformation is difficult (9)

TRANSPOSITION OF GREAT VESSELS WITH PULMONIC STENOSIS OR ATRESIA Figure 12 shows an increase in aortic blood flow and a reduction in the pulmonary blood flow and the effective pulmonary blood flow Similar to transposition of the great vessels without pulmonic stenosis the systemic and lesser circulations exist as separate units and a unilateral shunt does not exist (9)

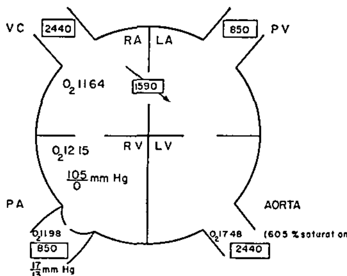


FIG 13 — Pulmonic stenosis with patent foramen ovale Circulatory findings

PULMONIC STENOSIS WITH PATENT FORAMEN OVALE This malformation has been described in detail (72 140 164) The circulatory findings are illustrated in Figure 13 There is no significant difference in the oxygen content of blood samples obtained from the right auricle and ventricle The peripheral arterial oxygen saturation is reduced demonstrating the presence of a right to left shunt The systemic flow in these patients is usually normal and the average effective and pulmonary artery flows are reduced No significant left to right shunt is

Diagnosis of transposition of the great vessels by catheterization is extremely difficult without advance knowledge of the nature of the malformation If the aorta is intubated it is helpful to turn the patient into the right oblique or right lateral position If the catheter lies anteriorly and in close proximity to the right ventricular outflow tract, the aorta is probably transposed The main value of catheterization in transposition of the great vessels lies in the recognition of the location of the shunt Here again it must be stressed that a unidirectional shunt cannot exist in transposition of the great vessels

Complete Transposition of Aorta with Overriding of Pulmonary Artery (183) Figure 17 demonstrates the catheterization

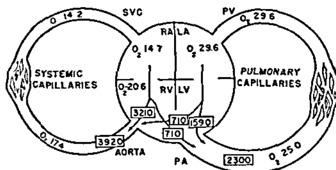


Fig 17 —Complete transposition of aorta with overriding of pulmonary artery Circulatory findings

findings The oxygen content of pulmonary arterial blood significantly exceeds that of right ventricular blood Since clinical findings in this malformation render the diagnosis of a patent ductus arteriosus unlikely the diagnosis of an overriding pulmonary artery can usually be made without difficulty

Defects of the Auricular and Ventricular Septums Defects of the auricular and ventricular septums are frequently associated with pulmonary hypertension (97 100) However Barber and co-workers (5) found no pulmonary hypertension in 21 patients with auricular defects who had undergone cardiac catheterization Burchell *et al* (38) found an increase in the pulmonary artery pressure in a patient with isolated ventricular septal defect who did not suffer from anoxemia Figures 18 and 19 illustrate that ventricular septal defects are usually characterized by a gradient in oxygen content from right auricular to right ventricular blood in auricular septal defects the gradient in the oxygen

Pulmonary Artery Flow Greater Than Systemic Flow or Pulmonary Artery Pressure Normal or Increased

Eisenmenger's Complex In this condition there is a high ventricular septal defect with overriding of the aorta and right ventricular hypertrophy The physiologic findings are illustrated in Figure 15 Pulmonary hypertension is present In some individuals pulmonary artery flow exceeds systemic flow (9 18) However the difference between the two rates of volume flow is usually slight The intracardiac shunt may be directed toward the left The vascular resistance of the pulmonary bed is increased As a result the systolic and diastolic pressure components recorded from the pulmonary artery are elevated Lequime and Charlier (127) Cosby *et al* (46) and Soulie *et al* (172) also reported catheterization studies in patients with Eisenmenger's complex

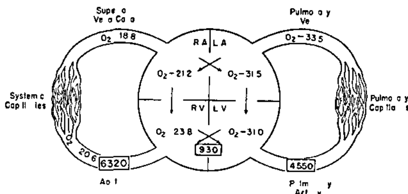


Fig 16—Transposition of great vessels with auricular and ventricular septal defects Circulatory findings

Complete Transposition of Great Vessels The first catheterization studies in this malformation were described by Campbell *et al* (41) An excellent description of this malformation is that by Lequime and Charlier (127) Catheterization findings as illustrated in Figure 16 are (*1*) right ventricular and left ventricular pressures are elevated (*2*) Due to the presence of an auricular septal defect the oxygen content of right auricular blood exceeds that of the superior vena cava (*3*) Since this patient also has a ventricular septal defect the oxygen content of right ventricular blood is higher than that of right auricular blood (*4*) The oxygen saturation of peripheral arterial blood is markedly decreased

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COMPLETE TRANSPOSITION OF AORTA WITH OVERRIDING OF PULMONARY ARTERY (183) Figure 17 demonstrates the catheterization

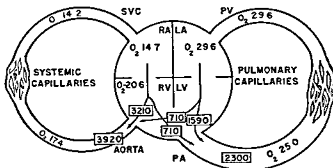


FIG 17 —Complete transposition of aorta with overriding of pulmonary artery Circulatory findings

findings The oxygen content of pulmonary arterial blood significantly exceeds that of right ventricular blood Since clinical findings in this malformation render the diagnosis of a patent ductus arteriosus unlikely the diagnosis of an overriding pulmonary artery can usually be made without difficulty

DEFECTS OF AURICULAR AND VENTRICULAR SEPTUMS Defects of the auricular and ventricular septums are frequently associated with pulmonary hypertension (97 100) However Barber and co workers (5) found no pulmonary hypertension in 21 patients with auricular defects who had undergone cardiac catheterization Burchell *et al* (38) found *an increase in the pulmonary artery pressure in a patient with isolated* ventricular septal defect who did not suffer from anoxemia Figures 18 and 19 illustrate that ventricular septal defects are usually characterized by a gradient in oxygen content from right auricular to right ventricular blood in auricular septal defects the gradient in the oxygen

Pulmonary Artery Flow Greater Than Systemic Flow or Pulmonary Artery Pressure Normal or Increased

Eisenmenger's Complex In this condition there is a high ventricular *septal defect with overriding of the aorta and right ventricular* hypertrophy The physiologic findings are illustrated in Figure 15 Pulmonary hypertension is present In some individuals pulmonary artery flow exceeds systemic flow (9 18) However the difference between the two rates of volume flow is usually slight The intracardiac shunt may be directed toward the left The vascular resistance of the pul

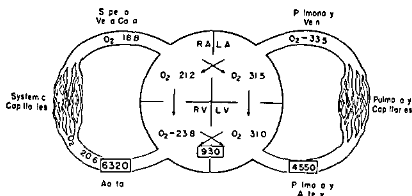


Fig 16—Transposition of great vessels with auricular and ventricular septal defects Circulatory findings

monary bed is increased As a result the systolic and diastolic pressure components recorded from the pulmonary artery are elevated Lequime and Charlier (127) Cosby *et al* (46) and Soulié *et al* (172) also reported catheterization studies in patients with Eisenmenger's complex

Complete Transposition of Great Vessels The first catheterization studies in this malformation were described by Campbell *et al* (41) An excellent description of this malformation is that by Lequime and Charlier (127) Catheterization findings as illustrated in Figure 16 are (*1*) right ventricular and left ventricular pressures are elevated (*2*) Due to the presence of an auricular septal defect the oxygen content of right auricular blood exceeds that of the superior vena cava (*3*) *Since this patient also has a ventricular septal defect the oxygen* content of right ventricular blood is higher than that of right auricular blood (*4*) The oxygen saturation of peripheral arterial blood is markedly decreased

content between caval and right auricular blood in some instances is not greater than that found in individuals without auricular septal defect They attributed this to the fact that the volume of blood passing through the two venae cavae is different that the flow of blood through the inferior cava is laminar that there is no adequate mixing of blood in the right auricle and that the direction of the shunt is not always from left to right Opdyke and co workers (62 133 150) have performed extensive studies on the dynamics of artificially produced auricular and ventricular septal defects in dogs Their studies contribute

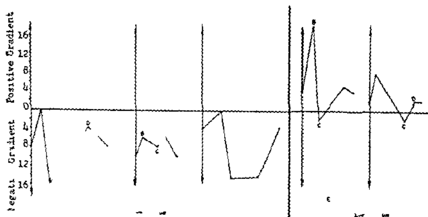


Fig 20 —Gradient between left and right auricular pressures during various phases of cardiac cycle (A to B) in various patients

significantly to the understanding of the dynamics of these malformations Calazel *et al* (40) as well as Cournand *et al* (51) and Brannon *et al* (31) have analyzed the pressure relationship in a series of patients with auricular septal defects

Figure 20 shows the gradient between left and right auricular pressures during the various phases of the cardiac cycle (points A to D) The gradient is called negative if the left auricular pressure is less than the right auricular pressure Conversely the gradient is called positive if the left auricular pressure is greater than the right auricular pressure Patients J D A J and A L had tricuspid atresia or pulmonic stenosis with an auricular septal defect Patients E T and K N had isolated atrial septal defects

The circulatory findings in Lutembacher s syndrome (mitral stenosis with auricular septal defect) are illustrated in Figure 21 There is a

content is between caval and right auricular blood In auricular as well as in ventricular defect the over all shunt is usually from left to right but in some instances depending upon the relative resistance in the pulmonary and systemic vascular bed the shunt may be from right to

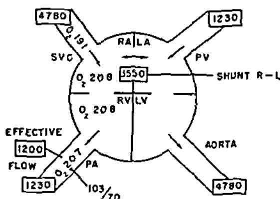


Fig 18 —Auricular septal defect Circulatory findings

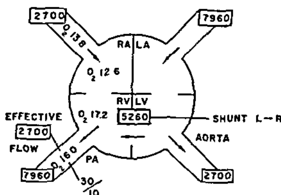


Fig 19 —Ventricular septal defect Circulatory findings

left Differential diagnosis between a patent ductus arteriosus and a high ventricular septal defect is sometimes difficult on the basis of catheterization studies alone since some of the oxygenated blood from the pulmonary artery may regurgitate into the right ventricle increasing the gradient between the oxygen contents of right auricular and ventricular blood Lason and Alvarez (123) from the Institute of Cardiology in Mexico performed 30 catheterizations on 25 patients with interauricular communications They found that the gradient in oxygen

single ventricle may be suspected if the oxygen content in the high pressure chamber exceeds that of right auricular blood by at least 3 vol % Diagnosis is particularly difficult if other malformations of the great vessels are associated with the presence of a single ventricle This is frequently the case To distinguish between cases with single ventricle in which the pulmonary artery arises from the rudimentary outlet chamber and those in which the aorta arises from this chamber calculations of the systemic and pulmonary flows are important If the pulmonary blood flow calculated from oxygen figures of the high pressure chamber is low it may be assumed that the pulmonary artery either

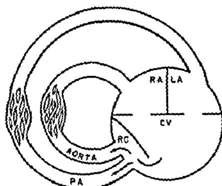


Fig 23 —Single ventricle with both great vessels arising from rudimentary outlet chamber Circulatory findings

originates from the rudimentary outlet chamber or that pulmonic stenosis is present On the other hand if the calculated pulmonary flow is high and the systemic flow is low the aorta probably originates from the rudimentary outlet chamber Figure 22 illustrates a case of single ventricle with the aorta arising from the rudimentary outlet chamber (9) and Figure 23 illustrates the dynamics in a case of single ventricle with both great vessels arising from a rudimentary outlet chamber

Truncus Arteriosus True truncus arteriosus is a rare malformation Miller *et al* (143) have studied a case of truncus aorticus solitarius and anomalous venous return

Soulie *et al* (172) described catheterization studies in patients with various types of truncus arteriosus They stated that diagnosis by means of catheterization is difficult that the pulmonary artery cannot be intubated that the pressure in the ventricle is elevated and that the oxygen content of blood in the main pressure chamber is increased

large shunt from left to right through the auricular septal defect and as a result the pulmonary blood flow is greatly increased (9) Calazel *et al* (40) have shown that in patients with Lutembacher's syndrome the left auricular pressure exceeds that in the right auricle

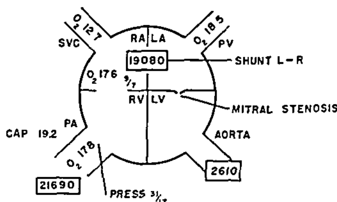


Fig 21 —Lutembacher's disease Circulatory findings

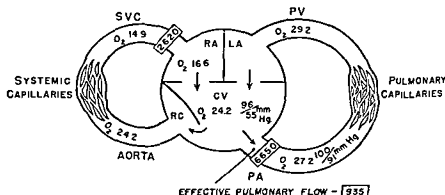


Fig 22 —Single ventricle with aorta arising from rudimentary outlet chamber Circulatory findings

Single Ventricle with Both Vessels Originating from Rudimentary Outlet Chamber Single Ventricle with Aorta Arising from Rudimentary Outlet Chamber These malformations are extremely difficult to diagnose by cardiac catheterization alone The presence of a

scribed the case of a 10 year old child in whom cardiac catheterization indicated the presence of a patent ductus arteriosus and pulmonary hypertension Dammann *et al* (56) described 4 patients in whom pressure in the pulmonary artery was at least equal to that encountered in the systemic artery Diagnosis of this interesting malformation may be made by intubation of the ductus or by comparing the oxygen saturation of blood in the right brachial artery and in one of the femoral arteries Due to reversed flow through the ductus the oxygen satura

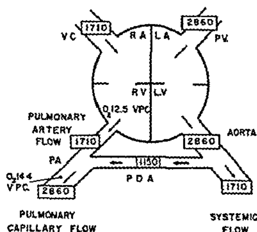


Fig 25 —Patent ductus arteriosus Circulatory findings

tion of femoral arterial blood is below that of right brachial arterial blood (9)

Lason *et al* (125) described catheterization studies in 8 cases of patent ductus arteriosus They believe that a definitive diagnosis of a patent ductus arteriosus by catheterization can be made only if the catheter enters the aorta through the ductus Levinson *et al* (129) believe that there is a specific local elevation in pulmonary systolic and diastolic pressure in patients with patent ductus arteriosus

Pulmonary Flow Equals Systemic Flow at Rest and Exercise

Isolated Congenital Pulmonary Stenosis (Fig 26) In most studies on this malformation (67 94 122 140 152 166) diagnosis was not confirmed by autopsy those by Marquis *et al* (140) are the exception There is no significant change in the oxygen content of blood samples

above that of auricular blood and equals the oxygen content of peripheral arterial blood They claimed that the catheter can be pushed into a large high pressure chamber without too much difficulty The findings in a case of physiologic truncus arteriosus are illustrated in Figure 24

PATENT DUCTUS ARTERIOSUS (Fig 25) The oxygen content of pulmonary artery blood *is greater than that of right ventricular blood* (9)

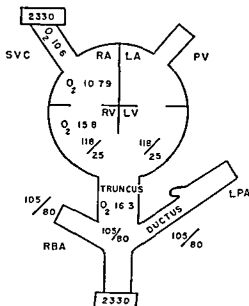


FIG 24 —Physiologic truncus arteriosus confirmed by autopsy Circulatory findings circulation to left lung through patent ductus arteriosus that to right lung through large bronchial artery Pressures in common ventricle and aorta approximately equal

Due to the presence of pulmonic insufficiency some of the oxygenated blood may regurgitate into the right ventricle simulating the presence of a ventricular septal defect The aortic flow is considerably greater than the systemic flow and the pulmonary capillary flow exceeds the right ventricular outflow Usually the flow through the ductus comprises about 40 per cent of the left ventricular output Findings have been reported on patients in whom the pulmonary arterial pressure exceeded that in the systemic circulation and the blood through the ductus coursed from the pulmonary artery into the aorta (9 50 114 145 184) In one patient there was an intermittent reversal of flow through the ductus (114) DuShane and Montgomery (69) have de

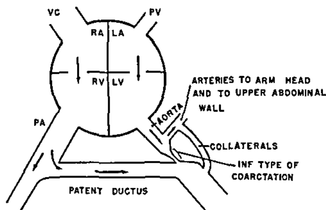


FIG 28 —Infantile type of coarctation of aorta Circulatory findings

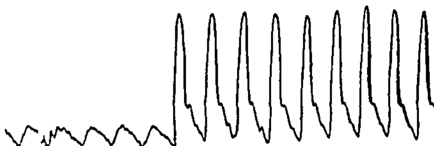


FIG 29 —Coarctation of aorta Pressure tracing obtained from catheter in aorta Sudden change in systolic pressure occurred as catheter tip passed through area of coarctation

pressure is also increased (140) Silber *et al* (166) found that patients with this malformation are able to maintain an adequate cardiac output at rest and with ordinary activity findings which agree with those described by Maraist *et al* (140)

COARCTATION OF AORTA In both the infantile and the adult type of coarctation catheterization has no diagnostic value unless there are

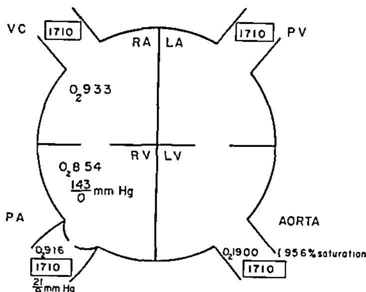


FIG 26—Isolated congenital valvulir pulmonary stenosis Circulatory findings

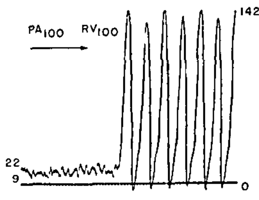


FIG 27—Valvular pulmonic stenosis Tracings obtained on withdrawal of catheter tip from pulmonary artery into right ventricle Pressure changes abruptly as tip passes through stenosed valve Pressure in right ventricle is very high

obtained from any chamber of the heart or the pulmonary artery Peripheral arterial blood is fully saturated demonstrating the absence of a right to left shunt Since there is no intracardiac shunt the systemic effective and pulmonary artery flows are equal There is a marked ele vation of the right ventricular pressure (Fig 27) The right auricular

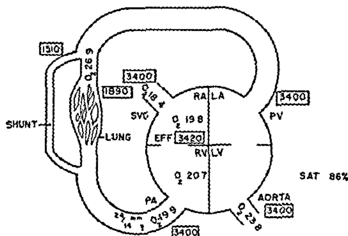


FIG 31 —Pulmonary arteriovenous fistula Cardiac output is normal arterial oxygen saturation is decreased Approximately 42 per cent of pulmonary artery flow is shunted through fistula

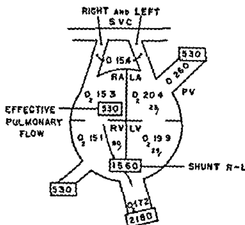


FIG 32 —Left superior vena cava entering left auricle Circulatory findings

ANOMALIES OF VENOUS RETURN Anomalies of venous return may result in either a right to left or a left to right shunt Patients in whom the superior vena cava drains into the left auricle and patients with pulmonary arteriovenous fistulas belong in the former category In patients with a systemic arteriovenous fistula and in those in whom all or several pulmonary veins drain into the right auricle or one of its tributaries

associated malformations such as patency of the ductus arteriosus (Fig 28) If the ductus enters the aorta below the coarctation the flow through the ductus is reversed (from pulmonary artery to aorta) Taylor *et al* (184) have described patients with this malformation and Soulie *et al* (171) reported the catheterization results in 2 cases of this malformation

It is sometimes possible on intra arterial catheterization to pass the

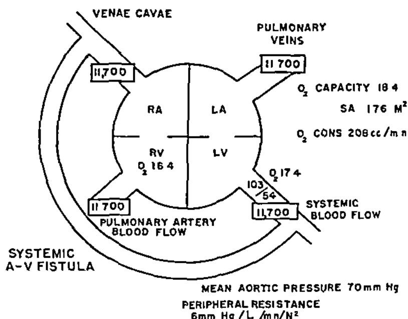


Fig 30—Peripheral arteriovenous fistula Cardiac output is increased and oxygen saturation in peripheral arterial blood is normal Right auricular pressure is usually normal

catheter tip from the thoracic aorta through the coarctation into the aorta distal to the stenosis (Fig 29) The tracing from the proximal portion of the aorta shows widening of the pulse pressure systolic hypertension and a peculiar double dicrotic notch which I have observed repeatedly on several similar occasions The tracing from the distal aorta shows the typical damped tracing previously reported (14)

The etiology of hypertension in coarctation of the aorta has been investigated by means of catheterization and other physiologic methods (14) It was concluded that the hypertension existing in coarctation of the aorta is not necessarily the result of renal factors

of the right to left shunt Figure 33 illustrates the findings in a patient in whom all the pulmonary veins drained into the superior vena cava A patent foramen ovale was also present The oxygen content of the blood in all cardiac chambers was identical and the pulmonary flow was markedly increased

Adaptation to Anoxia in Congenital Heart Disease with Cyanosis

One of the more interesting studies involving catheterization has been concerned with metabolic and circulatory adjustments to chronic

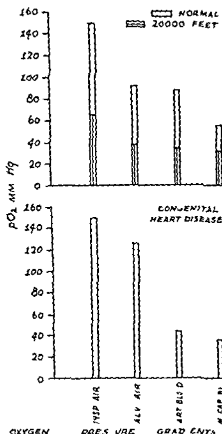


Fig 34 —Gradients in oxygen transfer system from inspired air to capillary blood in normal individuals at sea level and at high altitude and in patients with congenital heart disease of the cyanotic type (19)

the shunt is from left to right Anomalous drainage without shunt is present when there is a persistent left superior vena cava Extensive physiologic studies of this malformation have been performed (85 118) Hwang *et al* (112) described catheterization findings in a case of almost complete transposition of the pulmonary veins into the right atrium persistent left superior vena cava with associated interauricular

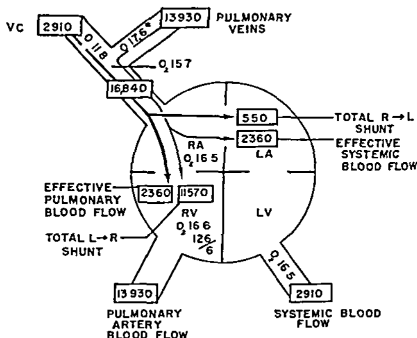


FIG 33 —All the pulmonary veins draining into superior vena cava Circulatory findings (85)

septal defect and pulmonary stenosis Catheterization studies on pulmonary arteriovenous fistula have been reported (3 57 85 139) Figures 30 to 33 represent diagrammatic outlines of the various malformations belonging in this category Denolin *et al* (57) as well as Baker and Trounce (3) described findings in patients with pulmonary arteriovenous fistula in whom the cardiac output was increased Figure 32 illustrates the findings in a patient with two superior venae cavae one of which drained *into the left auricle in addition* the patient had pulmonic stenosis and a ventricular septal defect The peripheral arterial oxygen saturation was decreased due to the presence

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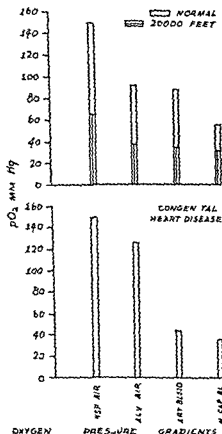


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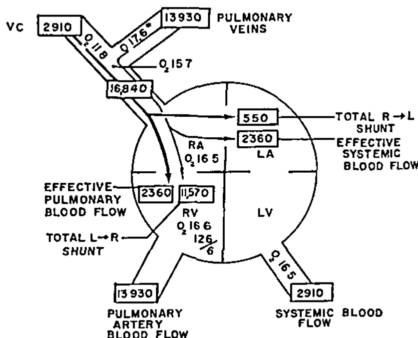


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result of decreased oxygen pressure in inspired air (Fig 34) In congenital heart disease with cyanosis the bicarbonate content of blood is reduced together with the carbon dioxide tension and the blood pH is maintained at normal levels (Fig 35) Catheterization studies also allowed investigation of the gradient in oxygen pressure from arterial to mean capillary blood which was found to be reduced in patients with congenital heart disease of the cyanotic type as well as in individuals exposed to high altitude (Fig 34) Havel and Watkins (106) found that children with cyanotic congenital heart disease have normal resting lactate and pyruvate plasma levels despite lowered arterial oxygen tension

Burchell *et al* (37) performed catheterizations on 20 patients with congenital heart disease of the cyanotic group Studies were performed at rest and during exercise They were unable to establish any relationship between circulation rate (the systemic blood flow) oxygen saturation and oxygen capacity of arterial blood It was apparent that polycythemia was not a uniformly necessary requirement for the well being of the hypoxemic patients suffering from congenital heart disease This confirmed the finding (19) of the relatively small role which polycythemia plays in reducing the gradient between the oxygen tension in arterial and mean capillary blood Burchell *et al* obtained no evidence that the increase in hypoxia resulted in increased pulmonary resistance

CATHETERIZATION IN ACQUIRED HEART DISEASE

Mitral Stenosis

A diagnosis of mitral and other valvular diseases can be made on the basis of a clinical examination alone However recent progress in the surgical treatment of mitral stenosis has renewed interest in the pathophysiology of this disease and catheterization study of patients in order to obtain more information on the possibility of operation on the mitral valve seems advisable Cardiac catheterization is also of interest in postoperative studies in order to evaluate the possible benefits of operation and the prognosis Clinical information had heretofore indicated disturbances in the pulmonary circulation accentuation of the pulmonary second sound increased prominence of the pulmonary vascular shadow and enlargement of the right ventricle all pointed to the presence of increased pressure in the lesser circulation

Bloomfield *et al* (22) were the first to describe increased right

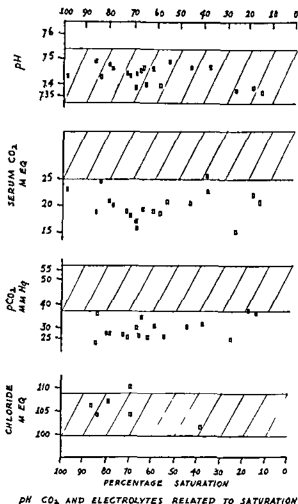


FIG 35—Cyanotic type of congenital heart disease Relations of pH CO electrolytes and oxygen saturation Shaded areas indicate normal range Serum CO and pCO are decreased proportionately and pH therefore remains within normal range (19)

hypoxemia of congenital heart disease The findings in these patients with those existing in individuals exposed to high altitude have been compared (19) In congenital heart disease with cyanosis the anoxemia is the result of the intracardiac shunt which increases the gradient of oxygen tension between alveolar air and arterial blood (Fig 34) In normal individuals exposed to high altitude the anoxemia is the

pulmonary resistance will remain Information on the state of the pulmonary vascular bed can be obtained by comparing the results in patients with mitral disease during rest and exercise (68 93 109) Most investigators agreed that the pulmonary artery pressure in mitral disease is elevated at rest rising still further during exercise Bayliss *et al* (6) found some correlation between exercise tolerance and the height of the pulmonary artery pressure patients with normal systolic pres-

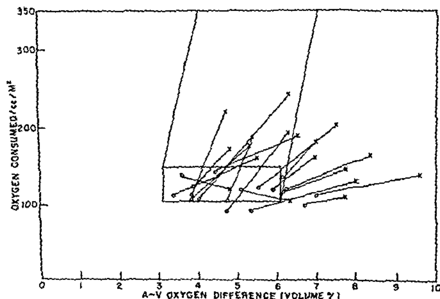


FIG 37 —Mitral stenosis Response to exercise Rectangle includes resting normal values for oxygen consumption and arteriovenous oxygen difference *in most* patients arteriovenous oxygen difference increased disproportionately to oxygen consumption (69)

sure being less incapacitated than those with raised pulmonary artery pressure However they described several exceptions to this rule There is no doubt that the primary factor responsible for the development of pulmonary hypertension in mitral stenosis is the mechanical obstruction offered by the diseased mitral valve However pathologic and physiologic studies have indicated that pulmonary vascular disease may be equally if not more responsible for the maintained elevation of pressure in lesser circulation Gorlin *et al* (93) for instance have shown that with lesser degrees of pulmonary hypertension the pulmonary artery pressure is increased in proportion to the pulmonary

ventricular pressure in patients with mitral stenosis Others (6 21 102) reported increased right ventricular and pulmonary artery pressure in mitral disease An elevation in the pulmonary artery pressure could be the result of increased pulmonary flow in the presence of fixed vascular

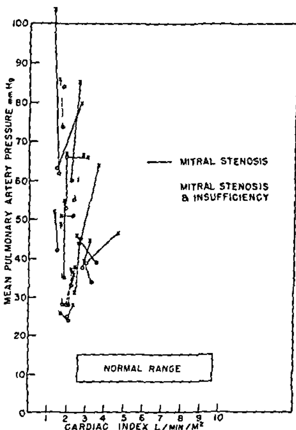


FIG 36—Mitral stenosis Relation of cardiac output to pulmonary pressure during exercise there is a proportionately larger increase in pulmonary artery pressure than in pulmonary blood flow (68)

pulmonary resistance or of an increased left atrial pressure and/or increased resistance of the pulmonary vascular bed An investigation of the factors which change pulmonary resistance in mitral stenosis is of great practical importance If operation on the mitral valve results in a fall in left atrial pressure alone without regression of pulmonary vascular changes the danger of pulmonary edema will be lessened but the danger of failure of the right side of the heart due to increased

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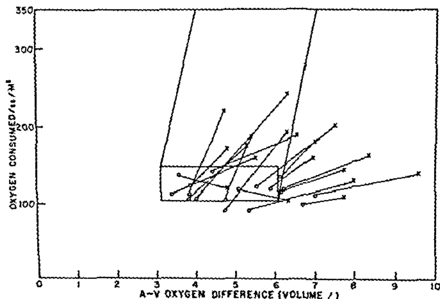


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capillary pressure and that the pressure gradient from the pulmonary artery to the pulmonary capillaries as well as pulmonary arteriolar resistance is normal This observation could not be confirmed by Calazel *et al* (40) who found no direct correlation between the height of the pulmonary capillary pressure and that of the pulmonary arterial pressure Pulmonary artery and capillary pressures with mitral disease were elevated at rest and rose further with exercise (Figs 36 and 37) Results

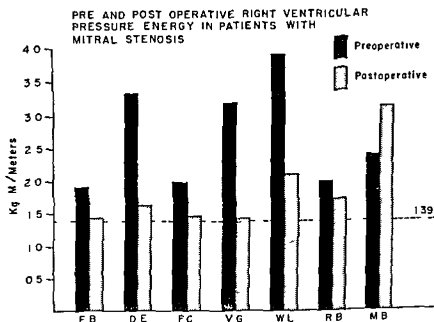


FIG 38 —Mitral stenosis Changes in ventricular pressure energy resulting from operation at stenosed mitral valve Except in patient M B pressure energy of right ventricle declined following operation

of postoperative studies have already shown that operation on the mitral valve leads to a diminution of pulmonary vascular resistance and a fall in pulmonary artery pressure (2 59 68) The physiologic findings indicating elevation in pulmonary artery resistance are borne out by anatomic observations (121 151)

Gorlin and Gorlin (91) developed standard hydrokinetic orifice formulas for calculating the size of the stenotic mitral valve These formulas are primarily of theoretic interest Clinical judgment is still the most important factor However the following conclusions from catheterization studies (68) may be taken into consideration (*1*)

Operation may be helpful in patients in whom rise in pulmonary artery pressure primarily results from resistance at the stenosed valve (2) Operation is not indicated in the presence of marked increase in the right auricular pressure and increased residual volume in the right ventricle

Operation on the mitral valve results in most instances in a fall in the pulmonary artery pressure (2 59) and a decline in right ventricular

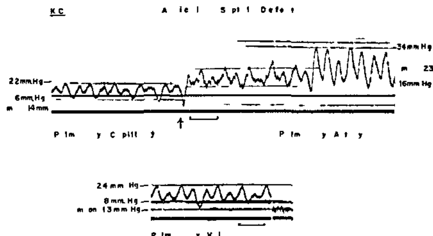


Fig 39 —Auricular septal defect Pulmonary capillary pulmonary artery and pulmonary vein pressures compared height of pulmonary capillary pressure is similar to that recorded from a pulmonary vein (140)

work (Fig 38) The changes in pulmonary vascular resistance are not uniform In many patients the postoperative clinical course cannot be correlated with physiologic findings For instance the pulmonary artery pressure may show a significant fall while the exercise tolerance remains poor It is entirely possible that a comparison of the pre and postoperative efficiency measurement of the whole organism during exercise may show a better correlation with the clinical results

Frequent reference was made in the preceding paragraph to the pulmonary capillary pressure This pressure is obtained as first shown by Hellems *et al* (107) by wedging the catheter into an end branch of a pulmonary vessel thus occluding it The pressures recorded

capillary pressure and that the pressure gradient from the pulmonary artery to the pulmonary capillaries as well as pulmonary arteriolar resistance is normal This observation could not be confirmed by Calazel *et al* (40) who found no direct correlation between the height of the pulmonary capillary pressure and that of the pulmonary arterial pressure Pulmonary artery and capillary pressures with mitral disease were elevated at rest and rose further with exercise (Figs 36 and 37) Results

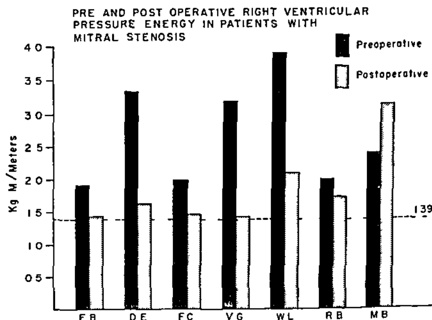


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of postoperative studies have already shown that operation on the mitral valve leads to a diminution of pulmonary vascular resistance and a fall in pulmonary artery pressure (2 59 68) The physiologic findings indicating elevation in pulmonary artery resistance are borne out by anatomic observations (121 151)

Gorlin and Gorlin (91) developed standard hydrokinetic orifice formulas for calculating the size of the stenotic mitral valve These formulas are primarily of theoretic interest Clinical judgment is still the most important factor However the following conclusions from catheterization studies (68) may be taken into consideration (*1*)

It was thought that such a comparison might be helpful in establishing whether or not the pulmonary capillary pressure resembled in shape or height the pulmonary vein or left auricular pressure They found that the average mean pulmonary capillary and pulmonary vein pressures exceeded the left auricular pressure by 2 mm Hg In patients in whom the left auricular pressure exceeded 10 mm Hg the gradient from pulmonary capillary to left auricular pressure was increased No relationship was found between the height of the pulmonary capillary and pulmonary artery pressures The gradient between these pressures was found to be independent of the height of the pulmonary capillary pressure These workers confirmed the findings of Dexter *et al* that the pulmonary capillary pressure was elevated in most patients with mitral disease (Fig 40)

Although the height of the pulmonary capillary pressure is significant the shape of the tracing is difficult to interpret I have never been able to obtain characteristic pulmonary capillary pressure tracings from normal individuals Gorlin *et al* (92) in a catheterization study of the factors regulating the pulmonary capillary pressure in mitral stenosis found that the occurrence of pulmonary edema in mitral stenosis does not depend upon the degree of stenosis directly but rather on the required rate of blood flow through the valve at any given moment In patients with severe mitral stenosis variations in the heart rate and cardiac output can lead to increase in the valvular flow rate and thus become the major determinants in the production of pulmonary edema They believe that the pulmonary capillary pressure is elevated in mitral disease in order to maintain the blood flow through the mitral valve In their opinion the mechanism of a sudden elevation in pulmonary capillary pressure is due to a momentary imbalance in ventricular output such that pulmonary blood volumes and pressures are increased They demonstrated that in patients with mitral stenosis a normal cardiac output can be delivered only at the expense of high capillary pressure The authors repeatedly mention the fact that to maintain increased rate of flow through the stenosed valve the pressure head in front of the mitral valve orifice must be elevated This dam and stream analogy frequently used to explain the elevation of venous pressure in congestive heart failure or in constrictive pericarditis is more teleologic than physiologic in this case it seems more accurate to state that on some occasions such as exercise or tachycardia the residual volume of blood in the left auricle increases leading to an elevation of the pulmonary vein and "capillary" pressures

through the catheter resemble in height those obtained from a pulmonary vein (Fig 39) Lagerlof and Werko (119) studied the variations in pulmonary capillary pressure in patients with cardiac arrhythmia and in patients with mitral stenosis and insufficiency Dexter *et al*

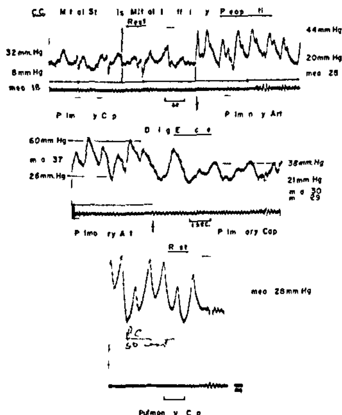


Fig 40—Mitral stenosis and mitral insufficiency Pulmonary artery and pulmonary capillary pressure tracings during rest and exercise Both pressures are elevated at rest and rise still further during exercise (68)

(58) compared the pulmonary capillary and the pulmonary artery pressure in normal individuals and in patients with various cardiovascular disorders They found that if the pulmonary capillary pressure rises above 25 mm Hg the gradient between pulmonary capillary and pulmonary artery pressure increases Calazel *et al* (40) compared pulmonary capillary pulmonary vein left and right auricular and pulmonary artery pressures in patients with auricular septal defects

output and the arteriovenous oxygen difference increased These workers consider the cardiac response to exercise adequate if the arteriovenous oxygen difference can be maintained within normal limits for the rate of oxygen consumption achieved When the arteriovenous oxygen difference exceeds normal limits the cardiac response is inadequate

The pulmonary artery pressure of normal individuals remains constant from rest to exercise according to Riley *et al* (160) and Hickam and Cargill Dexter *et al* (61) have shown that at oxygen consumptions exceeding 400 cc per minute per square meter of body surface pulmonary artery pressure rises more than pulmonary capillary pressure the pulmonary artery to pulmonary capillary pressure gradient increases This finding is in contrast to that obtained by most other investigators and is probably the result of difficulties in obtaining a steady state during exercise

In the conditions belonging to the hyperkinetic syndrome the cardiac output is increased This is the case in beriberi heart disease (39) anemia (30 165) peripheral arteriovenous fistula (45 85 190) possibly in certain types of pulmonary emphysema with anoxia (111) and in Paget's disease of bone (136) The cardiac output in hyperthyroidism is increased (136)

Congestive Failure and Digitalis

Cardiac catheterization is important in the study of heart failure and the action of cardiac glycosides if the findings are correlated with other physiologic studies such as the electrolyte balance and renal function tests In general the contributions of catheterization in this field derive from accurate pressure measurements and determinations of the cardiac output

Catheterization of the heart has confirmed studies which preceded the advent of this technic (103) There is no question that the cardiac output is decreased in most patients with cardiac failure (180) except in patients with the hyperkinetic syndrome McMichael (136) on the basis of catheterization studies defines heart failure as follows "The heart is failing when its capacity to increase output is seriously impaired and when output is only maintained at the expense of raised venous filling pressure Harrison's (111) definition of myocardial failure seems to be closely in line with the results obtained from recent catheterization studies of residual blood volume "The sine qua non of

Determination of Cardiac Output with the Catheter

Cournand summarized the problem first in 1945 (47) His most important conclusions were (1) Mixed venous blood may be obtained from the atrium in most instances provided the catheter is properly placed but occasionally auricular blood is poorly mixed (2) The arteriovenous oxygen difference is more constant than the arteriovenous carbon dioxide difference (3) Cardiac output should be calculated on the basis of the oxygen data (4) The maintenance of a stable physiologic state is of greatest importance Stead *et al* (182) performed catheterizations in 22 normal subjects and established normal figures for arteriovenous oxygen difference cardiac index and right atrial pressure they found that in anxiety the arteriovenous oxygen difference decreased and that tilting produced an increase in the cardiac index of about 23 per cent Richards (156) pointed out that like many physiologic functions cardiac output is the result of a great number of highly labile factors and noted that relatively mild disturbances may cause large changes in the cardiac output McMichael and Sharpey Schafer (138) examined the effect of posture on the cardiac output they demonstrated that on standing the arteriovenous oxygen difference increased and there was a significant fall in cardiac output Of particular importance are the observations of Cournand *et al* (52) on the circulatory effects of intermittent pressure breathing They found that using certain types of intermittent positive pressure breathing the cardiac output decreased The net filling pressure of the right ventricle decreased also during the phase of increased mask pressure and rose during the phase of decreasing mask pressure The net filling pressure of the right ventricle the pressure in the mask and the pressure in the ventricle moved therefore in the same direction Particularly noteworthy is the fact that when the mean right ventricular net filling pressure calculated for several entire respiratory cycles decreased the cardiac output also fell The influence of the heart rate on cardiac output was studied by Kelly and Bayliss (115) No relation was found between the degree of cardiac slowing and the increase in cardiac output following digitalis In normal hearts cardiac acceleration following atropine was accompanied by a fall in right auricular pressure and a rise in cardiac output There was no evidence that cardiac acceleration either depressed cardiac output or increased venous congestion

The effect of exercise on cardiac output in normal persons was studied by Hickam and Cargill (109) During exercise the cardiac

that the prime action of digitalis is on the ventricular muscle They also found that a fall in venous pressure could not be correlated with the magnitude of the increase in cardiac output Harvey *et al* (105) performed careful studies on the action of digitalis in left ventricular failure Before administration of the drug cardiac output was low pulmonary artery pressure was increased and the right ventricular and diastolic pressures and blood volumes were normal After digoxin cardiac output increased and pulmonary arterial pressure fell but pressure in the right ventricle at the end of diastole did not change The effect of digoxin was thus apparently a primary action on the left ventricular muscle resulting in a more complete emptying of this chamber It is noteworthy that the authors found no evidence in these studies of a peripheral venodilator action of digoxin as suggested by McMichael and Sharpey Schafer (137)

However McMichael (136) has recently considerably modified his stand "The view previously expressed that primary venous pressure reduction might be largely responsible for determining success or failure of digitalis therapy is no longer acceptable"

The effect of digoxin upon the heart in chronic cor pulmonale was studied by Ferrer *et al* (79) Digoxin produced a rise in cardiac output and a reduction in filling pressure and presumably a better emptying of the failing ventricle The increase in blood flow through a restricted pulmonary vascular bed was accompanied by a rise in pressure in the pulmonary artery After clinical improvement the cardiac output increased and the pulmonary arterial pressure was almost normal The observations of the various workers cited confirm the overwhelming pharmacologic evidence that digitalis has a primary myocardial action in heart failure An action on the peripheral venous circulation would explain the reduction in cardiac output in venous and right atrial pressure in normal dogs and in man The reduction in blood volume following administration of digitalis is further evidence of its possible peripheral action (66) A more quantitative examination of digitalis could possibly be achieved by more accurate determinations of its effects on the residual and diastolic blood volumes in the cardiac ventricles

Catheterization of the heart has made possible a critical analysis of the relationship between right atrial pressures and variations in cardiac output Stead and Warren (178) have shown that the output of the heart in the presence of adequate blood volume is determined by changes in ventricular relaxation and contraction which are independ

myocardial failure is to be found not in the cardiac output alone but in the completeness of cardiac emptying" Or as Richards (158) said One of the basic phenomena of congestive failure appears to be inadequate ventricular emptying during systole"

The condition of high output failure constitutes a true entity although the problem is probably more complex than was first thought. McMichael (136) found that in anemia with high output failure an increase in the venous pressure produced by transfusion caused a fall in cardiac output which made him believe that in the anemic heart any further increase in venous pressure decreases the output as would occur if the fibers had been stretched beyond optimal length In pulmonary heart disease with and without anoxia patients are encountered with normal with low and with high cardiac outputs (158) Variations in arterial oxygen saturations are probably responsible for these differences

It has been observed that in thyrotoxic heart failure the arteriovenous oxygen difference is often within the normal range and the cardiac output is increased in proportion to the metabolic rate (135) It is probably true that a heart with increased output can be in failure but the discussion will be on a philosophic rather than a physiologic level until it can be shown that the residual volume of blood in the hearts of patients with high output failure is increased A study of the measurements of the mechanical efficiency of these hearts is also indicated It will be of particular interest to see whether the increase *in the work of the heart of these patients is proportionately greater* than the increase in the oxidative cardiac metabolism if this should be the case the mechanical efficiency of these hearts would be elevated despite the existence of cardiac failure

Catheterization studies have confirmed the original observation of Harrison and Leonard (104) on normal dogs they found that digitalis causes a decrease in cardiac output Stead *et al* (181) studied the effect of intravenous injection of lanatoside C on the circulation in 22 patients with congestive failure The first measurable effect of the drug was on right atrial pressure the average fall during the first 60 to 120 minutes was 62 mm H O In most patients the cardiac output increased significantly There was no consistent change in oxygen consumption In patients with severe anemia who were in congestive failure with high cardiac output digitalis occasionally caused a still further increase in output Their data indicate that lanatoside C increases the output of the heart in the presence of normal rhythm and

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ent of fairly wide variations in atrial pressure Warren *et al* (189) produced an increase in blood volume by intravenous administration of 5 per cent albumin and physiologic saline solution The increase in blood volume consistently caused a rise in the atrial pressure The cardiac output the arterial blood pressure and the pulse rate however showed no consistent change It should be remembered however that it is the ventricular filling pressure and not the mean atrial pressure that determines the dynamic function of the heart

Traumatic Shock

The circulation in traumatic shock in man was thoroughly investigated by Richards (157 159) by means of cardiac catheterization One of the most significant findings was the recognition that there are a number of specific types of peripheral circulatory failure each with its own pattern of circulatory disturbance In secondary shock produced by skeletal trauma or hemorrhage the basic factor is loss of whole blood the resulting low blood volume leading to decrease in venous return in cardiac output and in arterial pressure The shock following severe burns has quite a different pattern There is hemoconcentration and consequently a loss of blood volume and a decrease in cardiac output there is an increase in peripheral resistance the right auricular pressure is maintained and in some cases even increased Apparently the primary reaction in burns is intense vasoconstriction both arterial and venous with decrease in venous return as the result Toxemia or hyperpotassemia may lead to myocardial failure

The response to abdominal injury differs in certain respects from the effects of skeletal trauma There is a decrease in right auricular pressure and cardiac output but hemoconcentration is always present Apparently all patients studied by Richards had peritonitis with acute exudate thus draining large amounts of serous fluid from the blood stream Arterial pressure was well maintained and the peripheral vascular resistance was high It is probable that shock resulting from abdominal injury is similar to that encountered in patients with pneumonia or malarial fever In these and other nonsurgical conditions the circulation fails with normal blood volume indicating some form of vascular collapse Richards in summarizing his results in shock said that while there are different injuries which lead to circulatory failure in different ways the essential finding in all of them appears to be an inadequate venous return of blood to the heart with diminished

cardiac output However he mentioned the fact that superimposed upon these events is the action of the vasomotor control which may be of great significance

Coronary Circulation and Myocardial Oxidative Metabolism Measured by Coronary Sinus Catheterization

Catheterization of the heart combined with Kety and Schmidt's (116) nitrous oxide method of determining the cerebral blood flow

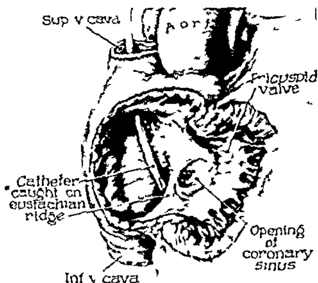


Fig 41 —Anatomic relationship of coronary sinus Difficulties in entering coronary ostium are illustrated by catheter caught on eustachian ridge (13)

suggested the possibility of applying these procedures to the determination of the coronary blood flow in man To accomplish this it was first necessary to obtain samples of coronary vein blood This problem was investigated after it had been shown that the procedure could be safely carried out in the experimental animal (13 70 90) The principle of the method consists in the introduction of an intracardiac catheter through the right auricle into the coronary sinus and the withdrawal of coronary sinus blood during or after saturation of the heart muscle with nitrous oxide

Purposeful catheterization of the coronary sinus is not always easy

The catheter is introduced into the coronary sinus in about 60 per cent of all attempted catheterizations (7 12) The reason for the difficulty may be seen from Figure 41 which shows that the catheter may be "caught" either at a prominent eustachian ridge or at a persistent thebesian valve Proof of entry into the coronary sinus is usually not difficult to obtain This consists in the unusual configuration of the catheter particularly in the right lateral position and the dark color of

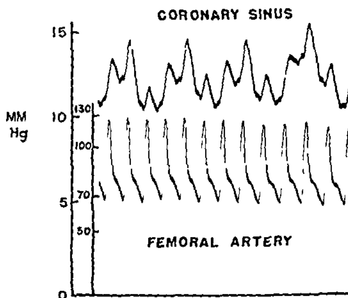


FIG 42 —Simultaneous pressure tracings from coronary sinus and femoral artery Coronary sinus pressure tracing shows respiratory fluctuations (7)

the blood withdrawn cardiac arrhythmias are infrequent when the catheter is in the coronary sinus The pressures obtained from the coronary sinus are lower than those usually obtained from the right ventricle (7) (Fig 42) Once the catheter has been placed in the coronary sinus the subject breathes 15 per cent nitrous oxide until the heart is saturated with it simultaneous samples of arterial and coronary venous blood are then drawn and the nitrous oxide contents during the saturation or preferably desaturation with the gas are plotted on linear graph paper (Fig 43) The coronary flow through a unit of heart muscle may then be calculated Gregg (95) has shown that the coronary sinus drains primarily the left ventricular muscle Consequently one measures with this method the coronary flow through a unit of the

left ventricular tissue only However although essentially all blood in the coronary sinus appears to arise from the left coronary artery not all the left coronary artery inflow leaves by this channel Furthermore Visscher (186) has shown that the oxygen content of the coronary sinus blood does not necessarily represent that of the other venous channels draining the myocardium It is important therefore to keep in mind that one measures the blood flow only through that unit of muscle which drains into the coronary sinus

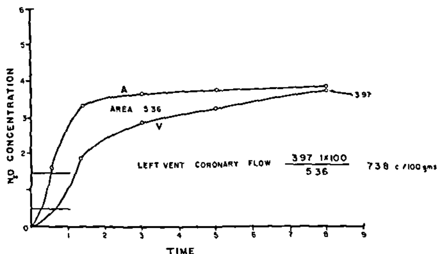


Fig 43—Arterial and coronary venous nitrous oxide curves obtained during desaturation Rising curves are obtained by subtracting each sample from nitrous oxide concentration at full saturation (13)

Using this procedure the myocardial oxygen usage per 100 Gm per minute may be calculated (7) The total left ventricular oxygen consumption can be obtained by approximating left ventricular weight from Smith s (168) tables The energy cost of the left ventricle may be computed from the oxygen usage The left ventricular efficiency may then be estimated

$$\frac{\text{Work of l ft ventricle}}{\text{Energy cost of left ventricle}}$$

The normal left ventricular efficiency is approximately 23 per cent (7) The assumptions necessary for these calculations have been discussed elsewhere (7 12, 13)

Figure 44 shows the average coronary blood flow through 100 Gm

of left ventricular muscle tissue (77 cc) the oxygen consumption for this unit of muscle (9 4 cc) and the average oxygen extraction (12 vol %) These figures indicate that the heart satisfies its metabolic requirements not by a large flow but by a large oxygen extraction The

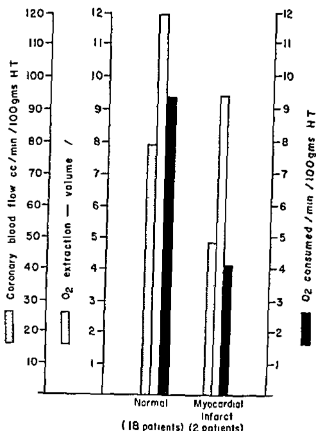


FIG 44 —Hyperthyroidism Findings in hyperthyroid individuals compared with those in normal ones (7)

normal heart extracts more oxygen than working skeletal muscle and the most important means by which the heart can cope with increased oxidative requirements is by increasing the coronary flow

However the coronary blood flow per unit of heart muscle in unanesthetized dogs is greater than in man probably because the metabolism of left ventricular muscle per unit of weight is determined by the ratio of surface area to left ventricular weight Since this ratio is

higher in small animals the cardiac metabolism per unit of weight is increased (175) (Fig 45)

The coronary blood flow may be normal or increased in three conditions belonging to the hyperkinetic syndrome (thyrotoxicosis

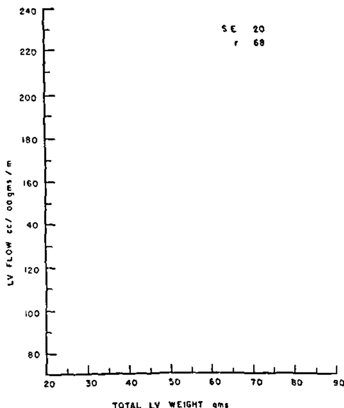


FIG 45 —Relationship of left ventricular blood flow per unit of left ventricular muscle to total left ventricular weight Note inverse relationship between total left ventricular weight and blood flow per 100 Gm (175)

anemia and peripheral arteriovenous fistula) In Graves disease the myocardial oxygen consumption per unit of weight per beat is normal despite the increase in total metabolism (7) (Fig 44) This is admittedly an unexpected result the findings are however in line with those of Dock and Lewis (65) In patients with mild anemia the coronary blood flow is increased in severe anemia the coronary blood flow may reach three times its normal value bringing the oxygen

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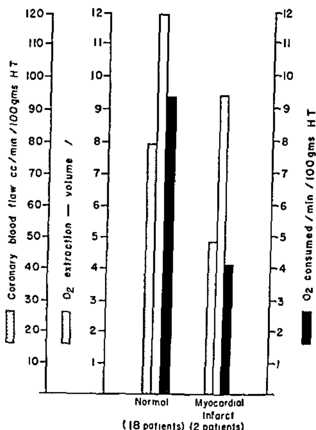


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CORONARY FLOW cc/MIN/100gms HT
O_2 EXTRACTION – VOL/
O_2 CONSUMED/MIN/100gms HT

NORMAL (18 patients)
HYPER TENSION (7 patients)
COARC TATION (6 patients)

Fig 47 – Comparison of findings in normal individuals in patients with essential hypertension and with coarctation of aorta (7)

Comparison of Coronary Resistance in Normal and in Hypertensive Patients

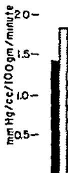


Fig 48 – Comparison of coronary resistance in normal individuals and in patients with hypertension (7)

consumption of the heart muscle to even higher than normal values (7) (Fig 46) In patients with peripheral arteriovenous fistula without cardiac failure but with large cardiac output the coronary flow and the oxygen consumption per unit of weight may be increased (7)

In hypertensive cardiovascular diseases coronary flow and myocardial oxygen consumption are normal (Fig 47) This suggests an in

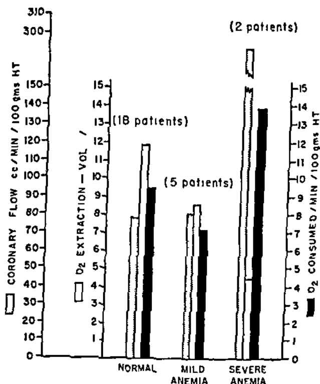


FIG 46—Anemia (mild and severe) Coronary flow is slightly increased in mild anemia in severe anemia coronary flow is trebled (7)

crease in the vascular resistance in the coronary bed (Fig 48) In contrast coarctation of the aorta is accompanied by an increase in the coronary blood flow and in the myocardial oxygen consumption (7) (Fig 47)

The findings obtained on myocardial oxygen usage and coronary blood flow in patients with essential hypertension indicate a completely different response of the heart subjected to chronic and acute increases in load respectively (7) When the heart is exposed to acute increases in

greater than in the normal heart and each fiber is supplied with a larger amount of blood (7) (Fig 50) The result is an increased flow through the individual capillary and increased irrigation of each individual myocardial fiber Dock also found that the capacity for coronary flow increases with the ventricular weight, as long as atherosclerosis spares the large arteries (64)

In patients with myocardial fibrosis coronary blood flow and oxidative metabolism are usually reduced (7) (Fig 51) In cardiac

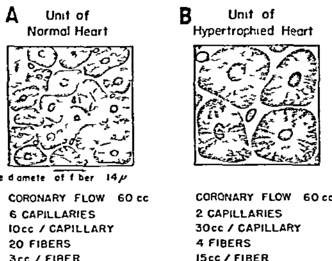


FIG 50—Cross section of normal (A) and hypertrophied (B) myocardium. Volume of blood coursing through each capillary of hypertrophied heart is greater than in normal heart consequently each fiber is supplied with larger amount of blood (7)

failure cardiac output and left ventricular work are decreased, but coronary flow is normal (7) (Fig 52) The normal or only slightly increased oxygen consumption per unit of heart weight in cardiac failure is interesting Since the work of the left ventricle is decreased, the maximal efficiency of the failing heart is diminished These findings indicate that there is a marked difference between the metabolic response of the failing heart *in vivo* and the failing heart under experimental conditions

Since the heart in failure seems to be unable to convert oxidative energy into useful work digitalis must, to be effective act to establish the link between energy consumption and energy liberation Stro-

load (exercise) the coronary blood flow and oxygen consumption per unit of weight increase (Fig 49) In the hypertrophied heart with a chronic increase in load the coronary blood flow and the myocardial

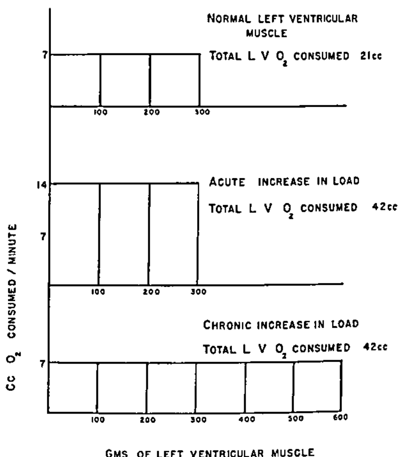


FIG 49 —Comparison of response of heart muscle to acute and chronic increase in load Acute increase in load results in increased oxygen usage per unit of fiber chronic increase in load results in rise in oxygen uptake of whole heart while oxygen consumption per unit of weight remains constant (13)

oxygen consumption per unit of fiber are normal because of the hypertrophy however the total coronary flow and the oxygen usage are increased This is an interesting example of the significant differences in the way the heart reacts to acute and chronic changes in load The volume of blood coursing through each capillary in the hypertrophic heart is

greater than in the normal heart and each fiber is supplied with a larger amount of blood (7) (Fig 50) The result is an increased flow through the individual capillary and increased irrigation of each individual myocardial fiber Dock also found that the capacity for coronary flow increases with the ventricular weight as long as atherosclerosis spares the large arteries (64)

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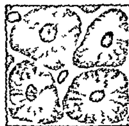


Fig 50—*Cross section* of normal (A) and hypertrophied (B) myocardium Volume of blood coursing *through each capillary of hypertrophied heart is greater* than in normal heart consequently each fiber is supplied with larger amount of blood (7)

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Coronary blood flow cc/min /100 gms HT

O_2 extraction — volume %

cc O_2 consumed /min /100gms HT

Normal (18 patients)

Hyperthyroidism (3 patients)

FIG 51 —Myocardial infarction Oxygen extraction and consumption as well as coronary blood flow per unit of left ventricular tissue are reduced (7)

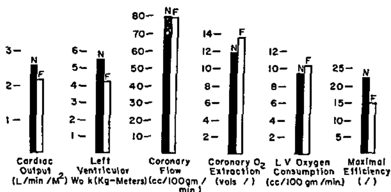


FIG 52 —Comparison of averages of data used in calculating left ventricular efficiency of normal individuals (N) and of patients with heart failure (F) Cardiac output and left ventricular work are decreased in failure but coronary blood flow is normal Oxygen consumption per unit of heart weight is only slightly increased Maximal efficiency of failing heart is diminished (7)

phanthus and digitalis preparations increase the work of the heart by raising cardiac output (Fig 53) They have no effect on the oxidative myocardial metabolism (7 16) increasing cardiac efficiency only by increasing cardiac work and not by reducing oxidative metabolism

Residual Volume of Blood in Right Ventricle in Normal and Diseased Hearts Estimated by Catheterization

The residual volume (volume of the blood remaining in a cardiac chamber during its isometric relaxation) and the diastolic volume

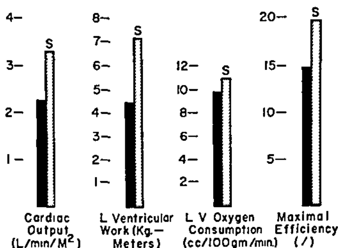


Fig 53—Effect of strophanthus K and digitalis preparations on work of failing heart its oxidative metabolism and its efficiency (7)

(volume of blood in that chamber during its isometric contraction) are of physiologic importance because the diastolic stretch plays an impor tant role in determining the dynamic and metabolic activity of the heart Furthermore the diastolic volume probably represents a blood reservoir which can be mobilized under stress In addition as Nylin (149) has shown prolongation of the circulation time in cardiac failure does not result from increased venous pressure and decreased cardiac output alone but is probably also caused by the dilution of the test substance in the large residual volume of the failing heart Therefore the ratio heart volume to stroke volume is a reliable measure of heart function Previous attempts to measure the residual or diastolic vol umes of the heart have relied primarily on x ray technics Cardiac

Coronary blood flow cc/min /100 gms HT

O2 extraction — volume %

cc O2 consumed /min /100gms HT

120 110 100 90 80 70 60 50 40 30 20 10

12 11 10 9 8 7 6 5 4 3 2 1

Normal (18 patients) Hyperthyroidism (3 patients)

FIG 51 —Myocardial infarction Oxygen extraction and consumption as well as coronary blood flow per unit of left ventricular tissue are reduced (7)

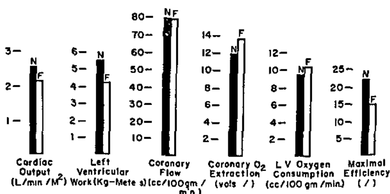


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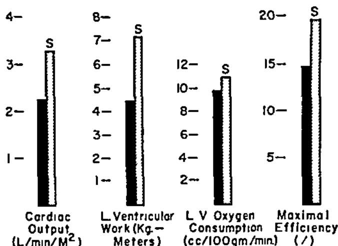


Fig 53 —Effect of strophanthus K and digitalis preparations on work of failing heart its oxidative metabolism and its efficiency (7)

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Coronary blood flow cc/min/100 gms HT

O_2 extraction — volume %

cc O_2 consumed/min/100 gms HT

Normal (18 patients)

Hyperthyroidism (3 patients)

FIG 51 — Myocardial infarction Oxygen extraction and consumption as well as coronary blood flow per unit of left ventricular tissue are reduced (7)

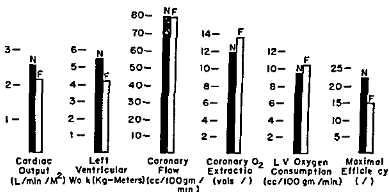


FIG 52 — Comparison of averages of data used in calculating left ventricular efficiency of normal individuals (N) and of patients with heart failure (F) Cardiac output and left ventricular work are decreased in failure but coronary blood flow is normal Oxygen consumption per unit of heart weight is only slightly increased Maximal efficiency of failing heart is diminished (7)

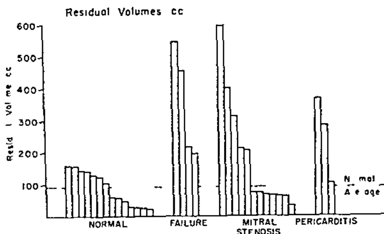


Fig 56 —Directly calculated values for right ventricular residual volumes obtained in normal and diseased hearts

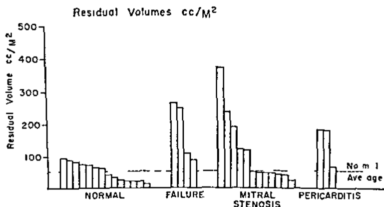


Fig 57 —Right ventricular residual volumes calculated per square meter of body surface in normal and diseased hearts In patients with myocardial failure residual volume is increased in mitral stenosis it is increased in some patients but normal in others in 2 patients with adhesive pericarditis it is increased in 1 patient with constrictive pericarditis it is normal

the blood and dye mixture is suctioned back through the automatic dye recorder and the concentration of Evans blue is photographically recorded (15) (Fig 55) From results obtained on an artificial model the residual volume of the right ventricle may then be estimated provided the volume of flow per minute is known Figures 56 and 57

catheterization with use of Evans blue for hemodynamic studies has suggested a different approach to the problem A double lumen catheter slightly modified from the conventional model is introduced in

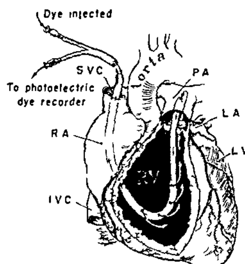


Fig 54 —Position of double lumen catheter in estimating residual volume of blood in right ventricle

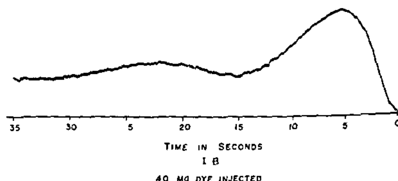


Fig 55 —Photographic recording of dye concentration in pulmonary artery after injection of Evans blue into right ventricle

such a manner that the opening of the distal twin catheter is in the main pulmonary artery while the five openings of the proximal twin catheter are in the right ventricle (15) (Fig 54) The pulmonary catheter is connected to the cuvette of a photoelectric dye recorder Evans blue is then injected from a calibrated syringe into the ventricular catheter

relationship of the heart *in vivo* it must be assumed that it is more correct to relate the diastolic volume of the heart to the initial fiber stretch than to attempt a correlation between initial filling pressure and initial fiber tension

Starling s work on the isolated heart consists of two parts One deals with the relationship between the diastolic volume of the heart and its work "An increased liberation of energy results from the contraction

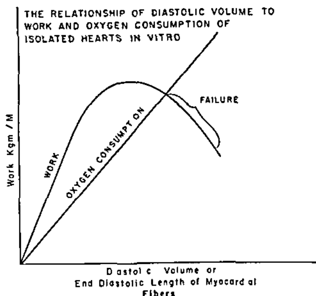


FIG 58 —Relationship of diastolic volume to work and oxygen consumption of acutely failing heart in heart lung preparations (7)

of the heart muscle when there is an increased diastolic volume" The other part of Starling s concept jointly formulated with Visscher deals with the relation between energy production and energy liberation of the heart (177) "The oxygen consumption of the isolated heart maintained under constant chemical and temperature conditions is determined by its diastolic volume and therefore by the initial length of its muscle fibers"

The first problem therefore deals with the relation between the diastolic volume of the human heart and its work (Fig 58) Does increased liberation of energy result from contraction of the heart muscle when there is an increased diastolic volume? Cardiac catheter

illustrate the results obtained with this method The average residual volume in normal individuals is 50 cc per square meter of body surface the ratio of residual volume to stroke volume is 1 75 Usually there fore the amount of blood remaining in the right ventricle after the systolic ejection exceeds the stroke volume In patients with myocardial failure the residual volume is greatly increased the volumes ranging from 90 to 280 cc per square meter of body surface (15) Because of the reduction in the systolic discharge the ratio residual volume to stroke volume is increased to an average of 13 6 In mitral stenosis the residual volume is increased in some patients but is normal in others The difference is probably the result of the presence or absence of right ventricular failure In 1 patient with constrictive pericarditis the residual volume was within normal limits but the ratio residual vol ume to stroke volume was elevated In 2 patients with adhesive peri carditis the residual volumes were markedly increased and the ratio residual volume to stroke volume was also elevated (15)

Regulation of Metabolic and Dynamic Functions of Human Heart in Vivo

At this point a correlation of some of the findings obtained by cardiac catheterization insofar as they pertain to the regulation of metabolic and dynamic processes of the heart seems indicated Most of our knowledge of the regulation of these processes is based on experiences on isolated hearts or on hearts of open chest animals under deep anesthesia Outstanding in this respect is the work of Frank (84) in Munich and of Starling in London (176) Frank using the frog heart established the fact that the stroke volume of the heart increases with increasing diastolic filling pressure Starling's concept differed from this formulation in one essential point Changes in ventricular filling and in diastolic stretch can take place without an increase in distending pressure or as Wiggers (191) puts it "The initial length of diastolic stretch is not necessarily accompanied by alterations in initial tension That this concept is correct for the right atrial–caval system has been shown by Opdyke *et al* (150) Even in the right ventricle which probably represents a less distensible system an increase of only 0 5 mm Hg in the mean of the net filling pressure in the right ventricle results in an increase of as much as 12 per cent in cardiac output (52) suggesting dissociation between diastolic volume and distending pres sures Therefore unless more is known about the volume pressure

consumption of the isolated heart maintained at constant chemical and temperature conditions is determined by its diastolic volume and therefore by the initial length of its muscle fibers" An investigation of this problem in man was impossible until a method was developed for determining the coronary blood flow and oxidative metabolism of the left ventricular muscle in man

If Starling's concept is correct both the diastolic volume and the oxidative metabolism of the heart should be increased in heart failure (Fig 58) However the oxygen consumption per unit of myocardium is normal or only slightly increased in patients with failure although the diastolic volume is increased (7) In Starling and Visscher's preparation (177) cardiac failure was always accompanied by increased oxygen consumption per unit of myocardium This they regarded as due to increased fiber lengths Such a relationship does not appear to be the case in chronic failure in man and therefore doubt must be cast on the application of this part of Starling's hypothesis

The results of studies on the effect of digitalis on the human heart are also not in line with the second part of Starling's concept (16) It is generally believed that digitalis decreases the diastolic volume of the heart and therefore as the failing heart diminishes in size the oxidative metabolism should decrease But as has been shown this is not the case the heart apparently develops greater facility in transmitting oxidative energy into mechanical work through more efficient utilization of energy (7) The difference between results obtained in chronic heart failure and acute heart failure as produced in the heart lung preparation is probably due to heart muscle adaptation to increased fiber tension An increase in the oxidative metabolism of a unit of fibers in chronic cardiac failure would be an uneconomic response of the heart since it would lead to significant reduction in efficiency particularly in the presence of decreased cardiac output

Liljestrand *et al* (130) showed that heart size does not increase appreciably during moderate exercise an indication that there is no significant increase in diastolic fiber length According to Starling and Visscher (177) the oxygen usage of the heart muscle per beat should remain constant under this condition But a series of tests which measured the myocardial oxygen usage from rest to exercise showed that the oxygen consumption of the heart per beat was significantly increased during exertion (10)

Clearly the application of the laws which govern the dynamic and metabolic functions of the heart muscle under experimental conditions

ization has made an investigation of this problem possible Cournand *et al* (52) studied the physiologic effect of *intermittent positive pressure* breathing on cardiac output in man and found that small changes in the filling pressure produced relatively large alterations in the cardiac output These findings confirmed Starling's concept because the change in mean net filling pressure is associated with changes in cardiac output moving in the same direction

However, if Starling's concept holds increased diastolic volumes should be found in all those conditions in which the stroke volume is increased such as the hyperkinetic syndrome and the normal heart during exertion McMichael (134) however noted that the response of the normal heart in moderate exertion does not follow Starling's principle but operates through other mechanisms nervous or humoral, tending to increase muscular contractility without increase in fiber length Stead and Warren (178) found (*1*) that a rise in atrial pressure by rapid infusion of saline solution does not cause a consistent rise in cardiac output (2) moderate reduction in atrial pressure by venesection does not cause a consistent fall in cardiac output and (3) a large arteriovenous fistula is usually accompanied by an increased cardiac output although there is no change in right atrial pressure

In patients with the hyperkinetic syndrome the cardiac output is increased and yet the atrial pressure is normal Stead *et al* (179) mentioned that in patients with atrial septal defects the pulmonary flow is markedly increased in the presence of large left to right shunt and yet the pressure in the left atrium is greater than that in the right According to them the cardiac output is regulated not by the height of the right atrial and venous pressures but rather by the degree of ventricular activity which can be increased by making the heart mechanically more efficient or by lowering the arterial pressure or by humoral stimulation of ventricular muscle or by reflex action on the ventricle

From evidence obtained in man so far it seems unlikely that increased diastolic volume results in increased liberation of energy under all conditions It is not clear what other causes determine the stroke volume and the force of contraction of the human heart *in vivo* This is a field of great interest but its solution must await the application of more accurate methods for the determination of the diastolic volume in man and the correlation of those data with pressures obtained in the cardiac chambers

The second part of Starling's concept deals with the relation between diastolic volume and oxidative metabolism (177) The oxygen

gated in several species of animals in normal and abnormal conditions The results have been contradictory Daly (55) for instance found that stimulation of the middle cervical ganglion and the stellate and upper thoracic sympathetic ganglions increased pulmonary arterial pressure Dirken and Heemstra (63) using the differential bronchial catheter demonstrated that the blood flow in the anoxic lung decreases while the circulation through the other lung increases thus confirming von Euler's observation that oxygen dilates the pulmonic arterioles much as carbon dioxide dilates the systemic ones On the other hand in the intact animal and man it is generally believed that mechanical rather than neurogenic factors play a far more significant part in the control of pulmonary blood flow and pulmonary arterial pressures Daly and Hebb (55) using cardiac catheters to inject a suspension of lycopodium spores into the pulmonary arterial tree of anesthetized dogs measured the pressure in the pulmonary artery and pulmonary capillaries the systemic pressure and the cardiac output and calculated the pulmonary arteriolar resistance from these data They found that lycopodium spores produce pulmonary hypertension by occluding pulmonary arterioles The spores do not reach the systemic circulation and if injected repeatedly will produce pulmonary hypertension of several weeks duration Experiments on isolated perfused lung preparations led to similar conclusions All of these experiments indicate that localized pulmonary emboli do not cause generalized pulmonary vasoconstriction The main evidence at the moment therefore is against a participation of the nervous system in the regulation of pulmonary blood flow

The convincing results of von Euler and Liljestrand (76) however call for further work in this line These investigators introduced a new concept of homeostatic mechanisms regulating the blood flow through the lung They found that moderate anoxia causes pulmonary hypertension in cats They concluded that the local effect of anoxia is part of a special mechanism totally different from an integrated nervous regulation which correlates local alveolar ventilation and circulation Thus low oxygen tension in isolated parts of the lungs will result in the shunting of blood away to better ventilated alveoli by means of a local mechanism controlling the arteriolar flow Motley *et al* (144) in catheterization studies extended the validity of these findings to normal man It is entirely possible that pulmonary vasoconstriction follows rapid changes in alveolar oxygen tension It is unlikely however that low blood oxygen tension has a similar effect In congenital heart dis

to the human heart *in vivo* is not necessarily justified The difference may well be due to the fact that in life the heart is exposed to numerous influences not present in the isolated preparations Furthermore heart failure in the isolated preparation develops in the short space of minutes or hours whereas chronic congestive failure develops gradually in the course of months or years Catheterization of the heart particularly catheterization of the coronary sinus would seem to be an ideal tool for developing more accurate methods with which to define the still mysterious laws governing the dynamic and metabolic functions of the human heart

CATHETERIZATION IN PULMONARY DISEASE

It is impossible to separate pulmonary vascular from cardiac disease since they are intimately related and affect each other However there are certain features which pertain primarily to the pulmonary circulation alone

Measurements of the output of the right ventricle and of the pressure in the pulmonary artery are the most important observations Pressure in the pulmonary vein is already described may be obtained by measuring the pulmonary capillary pressure (107) The validity of this measurement rests on two facts (*1*) there are no pulmonary or bronchial arterial anastomoses beyond the plugged artery and (*2*) the physical characteristics of the walls of the vessels which become part of the manometric system do not affect the pressure tracings (48) It was stated earlier that the findings of Calazel *et al* (40) confirmed the impression that the height of the pulmonary capillary pressure is similar to that of the left auricular and pulmonary vein pressures respectively

Cournand (48) has restated certain fundamental facts on the pulmonary circulation (*1*) An equal amount of blood flows through the lung and through the systemic circulation with momentary differences due to the rhythmic changes associated with breathing (*2*) Despite the fact that the pulmonary flow equals the systemic flow the pulmonary vascular bed is a low pressure system (*3*) The blood distribution through individual parts of the lungs depends on mechanical conditions rather than on control by the nervous system From time to time improvement as a result of autonomic nerve block procedures has been reported in patients with pulmonary embolism The possibility of nervous control of pulmonary vascular resistance has also been investi

gated in several species of animals in normal and abnormal conditions The results have been contradictory Daly (55) for instance found that stimulation of the middle cervical ganglion and the stellate and upper thoracic sympathetic ganglions increased pulmonary arterial pressure Dirken and Heemstra (63) using the differential bronchial catheter demonstrated that the blood flow in the anoxic lung decreases while the circulation through the other lung increases thus confirming von Euler s observation that oxygen dilates the pulmonic arterioles much as carbon dioxide dilates the systemic ones On the other hand in the intact animal and man it is generally believed that mechanical rather than neurogenic factors play a far more significant part in the control of pulmonary blood flow and pulmonary arterial pressures Daly and Hebb (55) using cardiac catheters to inject a suspension of lycopodium spores into the pulmonary arterial tree of anesthetized dogs measured the pressure in the pulmonary artery and pulmonary capillaries the systemic pressure and the cardiac output and calculated the pulmonary arteriolar resistance from these data They found that lycopodium spores produce pulmonary hypertension by occluding pulmonary arterioles The spores do not reach the systemic circulation and if injected repeatedly will produce pulmonary hypertension of several weeks duration Experiments on isolated perfused lung preparations led to similar conclusions All of these experiments indicate that localized pulmonary emboli do not cause generalized pulmonary vasoconstriction The main evidence at the moment therefore is against a participation of the nervous system in the regulation of pulmonary blood flow

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ease with severe arterial unsaturation pulmonary vasoconstriction may not be present

The *influence* of increased pulmonary blood flow on pulmonary artery pressure was discussed earlier Most investigators agree that a significant increase in cardiac output (to three times its basal level) can occur without changes in pulmonary artery pressure (109 160) After pneumonectomy the flow through the remaining lung is twice the flow through one lung of a normal individual (48) During mild exercise the rate of flow through the single lung exceeds that observed in each lung of normal subjects during severe exercise (48)

Pulmonary Circulation in Cor Pulmonale

Cor pulmonale is defined as isolated enlargement with or without failure of the right ventricle secondary to diseases of the lungs or pulmonary arteries (11) The earliest and occasionally the only sign of cor pulmonale is elevated pulmonary artery pressure Acute cor pulmonale is most frequently due to pulmonary emboli Chronic cor pulmonale is caused by chronic lung diseases which gradually impinge on and reduce the pulmonary vascular bed Rarely diseases of the pulmonary arteries or arterioles may result in cor pulmonale The reduction in the pulmonary vascular tree associated with chronic disease of the lungs or pulmonary arteries causes interruption of two closely related physiologic processes (*1*) Because blood flow has to be maintained through a reduced cross sectional area to sustain life pulmonary artery pressure pulmonary resistance and the work of the right side of the heart must increase Right ventricular hypertrophy follows and finally with increased venous pressure failure of the right side of the heart appears (*2*) Impingement on the vascular tree in chronic lung disease also reduces the area through which oxygen diffusion may occur In addition certain lung diseases cause thickening of the capillary membrane of the alveoli with further interruption of oxygen diffusion

The shunts occurring in pulmonary disease differ from those in congenital heart disease In pulmonary disease the shunting of blood within the lung takes place because part of the venous blood is not exposed to well ventilated alveoli and therefore does not reach full saturation An estimate of the shunt created by poor ventilation-perfusion relationships may be obtained by the methods of Riley *et al* (161)

In patients with accentuated second pulmonic sound and x ray

evidence of enlargement of the pulmonary arteries and right ventricle catheterization of the right side of the heart may yield valuable information If cyanosis is present it may be possible to rule out congenital heart disease and an increase in the pulmonary artery pressure suggests an early diagnosis of cor pulmonale The determination of the pulmonary capillary pressure is of great importance in distinguishing (1) between pulmonary hypertension due to pulmonary changes alone and (2) between pulmonary hypertension resulting primarily from mitral or aortic valvular disease or from left ventricular failure The pulmonary capillary pressure is normal in the first group but elevated in the second To distinguish the three types of cor pulmonale (that due to emphysema that due to pulmonary fibrosis and that due to pulmonary vascular disease) catheterization of the heart should be combined with other physiologic function tests such as spirography and pneumotachography

Rose *et al* (162) studied the difference in histamine content between arterial and mixed venous blood in normal individuals and in patients with asthma They found little difference in normal subjects but in patients with asthma increased arterial histamine levels and thus an increased difference between arterial and venous histamine levels

CATHETERIZATION IN RENAL DISEASE

Catheterization of the renal vein in man is performed primarily to learn the oxygen consumption of the human kidney or to determine the plasma extraction ratio of substances partially or completely removed from the plasma during one circulation through the kidney

Plasma Extraction Ratio

The extraction ratio is calculated from the equation Plasma extraction ratio $= \frac{A - V}{A}$ where A is the concentration in systemic arterial or venous blood and V is the concentration in renal vein blood If a substance is completely cleared by the kidney and if as a result of this the concentration of the substance in the renal vein is zero the extraction ratio is 1 The higher the concentration of a substance in renal vein blood the lower will be its extraction ratio The method of catheterizing a renal vein to determine the extraction ratio of any substance suffers from the limitation that renal vein blood must not be

drawn on the left side of the body in either dog or man because in some instances significant quantities of nonrenal blood may enter the vein close to the hilus via the spermatic or ovarian veins (169) Furthermore precautions must be taken not to contaminate the renal vein blood with blood from the inferior vena cava Finally procaine must not be used as a local anesthetic since it and related compounds react in the p aminohippuric acid (PAH) method and increase the venous blank significantly To avoid errors resulting from very low concentrations of PAH in renal vein blood Smith (169) determines blanks in both arterial and venous blood

Usually the effective renal plasma flow may be determined without intubation of the renal vein on the basis of the following equation

$$\text{Effective renal plasma flow} = \frac{UV}{P} \text{ of diodrast or PAH respectively}$$

This procedure however is valid only when the extraction ratio of diodrast or PAH (E_{PAH} or E_D) is close to unity In the presence of renal disease in which there is interference with tubular function a determination of the effective renal plasma flow using PAH or diodrast clearances is not accurate Smith (169) on the basis of experiments of his own and of collected data takes the average normal extraction ratio of diodrast (E_D) and the extraction ratio of PAH (E_{PAH}) in man as 92 per cent The blood which is not cleared by the excretory system of the kidney therefore represents no more than 8 per cent of the total renal blood flow

The technic of catheterization of the renal vein is described in the literature (25 188) It is relatively simple but I have found it advisable to use a special long catheter without a sharp bend

Sirota (167) found significant reductions in E_{PAH} in the early stages of spontaneous diuresis in 4 patients recovering from oliguria caused by inhalation of carbon tetrachloride He attributes the decreased extraction of PAH to tubular damage caused by anoxia resulting in increased tubular permeability Breed and Maxwell (32) also observed a patient with oliguria who was suffering from post transfusion reaction and found that E_{PAH} was reduced to 0 06 It is entirely possible that in other types of anuria caused by various compounds such as methemoglobin and mercurial compounds the E_{PAH} is greatly reduced probably as a result of back diffusion of PAH through the tubules (8) Bradley and Bradley (25) found no changes in E_{PAH} during abdominal compression indicating the absence of a juxtamedullary diversion of the blood

Cargill (42) has studied extensively the effect of renal disease on E_{PAH} and found that it remains within the normal range until renal damage is moderately advanced Bradley *et al* (27) also studied the extraction ratios of PAH in various forms of renal disease like Cargill they found that E_{PAH} was greatly reduced in the acute phase of glomerulonephritis making measurement of renal plasma flow by the PAH clearance method grossly inaccurate They concluded that the renal blood flow was actually in excess of normal in the acute phase of glomerulonephritis and that the reduction in the E_{PAH} denotes perfusion of a large mass of nonextracting renal tissue The extraction of PAH is also decreased in the chronic phase of glomerulonephritis During the terminal phase of glomerulonephritis the reduction in extraction ratios of PAH was even more significant

In pyelonephritis the PAH extraction was reduced in the 3 patients in whom it was determined In contrast its extraction ratio was normal in proteinuric nephrosis In benign nephrosclerosis extraction of PAH was high despite the fall in the maximal tubular excretion of that substance This suggests that blood perfuses only normally functioning tissue and does not flow to abnormal or dying tubules such as are present in inflammatory diseases of the kidney In malignant nephrosclerosis E_{PAH} was reduced indicating perfusion of nonfunctioning tissue

Edelman *et al* (71) studied the extraction ratios of PAH in patients with chronic congestive heart failure and found it to be decreased

Renal Oxygen Consumption

Warren *et al* (188) were the first to determine the renal oxygen consumption by means of renal vein catheterization The renal arteriovenous oxygen difference in 8 patients ranged from 1 9 to 2 8 vol % As one might expect the oxygen content of mixed venous blood was much lower than that of renal vein blood Cargill and Hickam (43) measured renal oxygen consumption in unanesthetized human subjects by renal vein catheterization The mean value for renal oxygen extraction in the normal subject was 1 42 vol % the mean renal oxygen consumption 16 cc per minute They found decreased oxygen consumption in patients with nephrosclerosis chronic glomerulonephritis and chronic pyelonephritis Since oxygen extraction in these patients was normal the decrease in oxygen consumption was caused by a reduction in flow Extraction of oxygen was decreased in patients with acute and

subacute pyelonephritis despite normal or increased renal blood flow These authors felt that renal oxygen consumption depends upon the relative proportion of tubular tissue actively functioning in the formation of urine from glomerular filtrate Therefore it seemed logical to them to expect renal oxygen consumption to vary with filtration rate as long as the amount of functioning tubular tissue remains unchanged Their data show good correlation between the glomerular filtration rate and the rate of oxygen utilization It seems more logical however to relate renal oxygen consumption to the maximal tubular excretory capacity of PAH

Edelman *et al* (71) measured the renal oxygen consumption of normal individuals and of patients in cardiac failure by means of renal vein catheterization The mean oxygen consumption in controls was approximately 15 8 cc per minute a finding in agreement with that reported by Cargill and Hickam Figures obtained for patients in congestive failure were lower Clark and Barker (44) found a mean of 6 2 cc per 100 Gm of normal kidney tissue per minute Bradley and Halperin (26) found renal oxygen consumptions in 5 normal individuals ranging from 6 to 14 cc per minute Since in cardiac failure the tubular excretory mass is probably normal the reduced renal oxygen consumption may represent a generalized decrease in renal metabolism

Renal Vein Pressure

Catheterization of the renal vein has also made possible a determination of renal vein pressure Maxwell *et al* (141) reported an average renal venous pressure in 17 normal subjects of 10 to 14 6 mm Hg In patients with congestive failure with persistent edema renal vein pressure was significantly elevated to a mean of 22 4 (mean normal 11 7 [169]) Blake *et al* (20) found that if the renal venous pressure of anesthetized dogs is increased to the range of 21 to 27 mm Hg sodium and water reabsorption by the renal tubules increases with no significant change in filtration rate or renal blood flow Farber *et al* (77) reported that an increase in inferior vena cava pressure in man produced by obstruction of that vessel above and below the entrance of the renal veins causes a significant decrease in the excretion of water and sodium renal plasma flow and glomerular filtration rate are also reduced but for a shorter period This indicates that renal hemodynamic changes are not necessary for the change in electrolyte excretion

MEASUREMENT OF HEPATIC FLOW

Hepatic flow may be measured by applying the Fick principle This has been accomplished by catheterization of a hepatic vein and infusion of the dye bromsulfalein (BSP) (28) The concentration of BSP in the blood entering the liver is determined by an analysis of the dye in peripheral arterial or venous blood The concentration of BSP in the blood draining from the liver can be determined by withdrawal of blood through the catheter inserted into a hepatic vein The total amount of BSP removed by the liver can be indirectly determined by infusing the dye into a peripheral vein at such a rate that its blood level remains constant Under these conditions the infusion rate equals the hepatic removal rate provided the extraction of BSP depends entirely upon hepatic activity By this method it has been found that the blood flow through the liver of normal man is approximately 100 cc per 100 Gm of liver tissue or 1 497 cc per 1 73 square meters of body surface

A different method has been employed by Myers (146) Using the method of Lipscomb and Crandall (132) he employed urea for the measurement of hepatic blood flow Urea has all the qualifications for a test substance in estimating liver blood flow It is produced in the human organism only by the liver and once formed is not converted into other compounds It is highly diffusible and since the level of urea in arterial blood is generally constant for several hours under conditions of fasting it must be lost from the body at the same rate as it is formed the total urinary excretion of urea under such conditions therefore approximates its hepatic formation Consequently liver blood flow can be calculated by means of urea on the same principle as the calculation of hepatic blood flow with BSP However Myers admits that the estimation of hepatic blood flow by the urea method has several disadvantages The technic is an extremely meticulous one because of the small arteriovenous urea difference In his opinion the main usefulness of the urea method has been to demonstrate that the fundamental assumptions utilized in the dye method are correct this appears to be the case because values for hepatic flow obtained by the urea method are similar to those obtained by the dye method Myers found average splanchnic oxygen consumption to be 42 cc per minute per square meter this comprises 24 per cent of the total oxygen consumption

Many studies have used the dye method and catheterization of one

of the hepatic veins to determine hepatic blood flow Bondy *et al* (24) studied the role of the normal human liver in carbohydrate metabolism both in the basal state and after intravenous administration of glucose They found that under fasting conditions the splanchnic system releases glucose to the circulation at a mean rate of 3 5 mg per minute per kilogram of body weight Of this approximately 7 per cent can be accounted for on the basis of gluconeogenesis from protein The hepatic glucose production could account for a mean of 70 per cent of the total normal basal metabolic requirement of the patients After intravenous glucose injection there is an immediate retention of glu cose by the liver However as the arterial glucose level falls the glucose is again released from the splanchnic circulation

Myers *et al* (148) compared the magnitude of the hepatic circula tion with the total systemic flow in patients with hyperthyroidism They found that the rate of splanchnic metabolism as judged by oxygen con sumption was increased to a level in excess of the average metabolic rate of the body This was primarily the result of a high oxygen extraction in the presence of normal splanchnic flow In this case the response of the liver to thyroid hormone differs from that of the heart the oxidative metabolism of the heart in hyperthyroidism being normal The blood flow through the brain is normal in hyperthyroidism and cerebral oxy gen consumption is not increased (163) whereas renal blood flow is elevated (142)

Myers and Hickam (147) studied the hepatic flow in 13 patients with heart failure of various degrees and of various etiologies and found a significant reduction in hepatic flow The decrease in hepatic flow was roughly proportionate to the decrease in cardiac output Clearance of BSP by the liver was reduced in patients with cardiac failure The hepatic arteriovenous oxygen difference was increased In cardiac failure the hepatic flow totalled on the average 24 ±7 per cent of the cardiac output in normal controls 20 ±4 per cent Average hepatic oxygen consumption in cardiac failure was normal despite the decrease in hepatic flow the result of the compensatory increase in the hepatic *oxygen extraction*

Culbertson *et al* (53) estimated changes in the hepatic flow occur ring with changes from recumbent to upright position They found that the hepatic flow decreased in 6 normotensive and 12 hypertensive sub jects after passive tilting into the upright position Hepatic flow failed to change regularly in 6 subjects after immersion of a hand in ice water for 1 minute These findings confirm the impression that active vaso

constriction occurs in splanchnic organs in addition to the kidneys when human subjects are tilted into the upright position Wilkins *et al* (194) studied the effect of splanchnic sympathectomy on hepatic blood flow After sympathectomy reductions of hepatic blood flow in hypertensive patients tilted into the upright position were associated with sizable decreases in arterial pressure and little change in average hepatic portal resistance Before splanchnic resection reduction in hepatic blood flow in the upright position occurred with little change in pressure and increases in hepatic blood flow They concluded that the splanchnic sympathetic nervous system mediates the hepatic portal vasoconstrictive response to the upright posture in hypertensive as well as in normal subjects

Bradley *et al* (29) investigated hepatic flow and hepatic BSP and oxygen extraction in patients with portal hypertension before and after portacaval anastomosis Hepatic flow fell after operation while BSP and oxygen extraction increased These effects were probably the result of a decrease in pressure in the portal system

Hepatic flow after ligation of the hepatic artery for portal hypertension has been studied in 1 patient (155) There was only a slight decrease in hepatic flow and no change in hepatic oxygen consumption indicating that most of the flow through the liver is through the portal vein and that an appreciable fraction of the oxygen supply to the liver is provided by the portal venous blood

Hepatic Sinusoid Pressure

Of particular interest are the studies by Friedman and Weiner (86) on the estimation of the hepatic sinusoid pressure in anesthetized dogs by means of the catheter The principle of the method is similar to that described by Hellems *et al* (107) in estimation of pulmonary capillary pressure A catheter is wedged into a division of the hepatic vein after blocking this vessel the pressure is determined through the catheter This pressure is the hepatic sinusoid pressure because there is a direct connection between the tip of the catheter and the sinusoid bed via a static column of blood Friedman and Weiner introduced a catheter into the splenic vein as well and wedged it into an intrahepatic portal vein branch Portal vein pressures were also determined Using this technic Friedman and Weiner found that the pressure in the occluding hepatic vein catheter was consistently higher than that registered from the occluding portal vein catheter This pressure relationship agreed

with the observations of others on occlusive pressures obtained with catheterizations Using the midpoint between occluding hepatic and portal vein catheters an average value for sinusoid pressure of 11 cm H_2O was found Undoubtedly this procedure will be used on normal individuals and on patients suffering from portal hypertension

As stated in the introduction of this review the main emphasis has been placed on dynamic problems and no attention has been paid to such important fields as in the recording of cavity potentials The papers of Goldman *et al* (88) and of Levine and Goodale (128) contain most of the references pertaining to this subject

Concluding Remarks

The first stage of the catheterization era has come to an end During this time the problems concerned with cardiac output and intracardiac pressures have been successfully dealt with It is hoped that during the second era the catheter may be utilized as a tool to explore fields of even greater importance such as the relationship between metabolic and dynamic function of the human myocardium or the intermediary metabolism of the normal and failing human heart

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Portal Hypertension and Its Treatment

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CHRONIC portal hypertension results from a block in the portal system affording impedence to blood flow The syndrome of portal hypertension commonly known as Bantis syndrome is well known It consists of congestive splenomegaly secondary anemia leukopenia thrombocytopenia and a history of attacks of gastrointestinal bleeding or demonstrable evidence of the presence of esophageal varices Cases of portal hypertension may be classified in two groups depending upon the site of portal block (*1*) intrahepatic, for example due to cirrhosis of the liver and (*2*) extrahepatic in which the liver is normal but there is a block in the portal vein itself or its radicals outside the liver The extrahepatic group represents approximately 30 per cent of the cases and in our experience the site of portal block is regularly confined to the portal vein itself the result of atresia thrombosis or cavernomatous transformation

The extrahepatic collateral venous channels which nature develops to by pass portal blood around the site of portal obstruction in patients having chronic portal hypertension are familiar to all Hematemesis that dreaded sign of serious disease places due emphasis upon the importance of the coronary esophageal circuit of collateral veins The sudden rupture of an esophageal varix constitutes an ever present threat of which Snell (29) said The control of hematemesis remains a most

serious problem Only about 20 per cent of patients [with cirrhosis of the liver] survive one year after their first hematemesis the other 80 per cent die"

Preble (26) in a postmortem study of 60 cases of cirrhosis of the liver in which death resulted from gastrointestinal hemorrhage was able to demonstrate the presence of esophageal varices in 80 per cent of the cases Furthermore the exact point of rupture of the varix was noted in 50 per cent of these

Kegaries (16) gives an account of the anatomy of the esophageal veins and the nature of the connection between the portal and the systemic circulation in 16 injected specimens having esophageal varices The interesting findings were as follows

(1) A periesophageal plexus as described by anatomists was not demonstrated in its place were found three or four longitudinal venous trunks with few or no cross anastomoses

(2) The submucosa of the esophagus on the other hand was found to be richly supplied with veins These veins however were very poorly supported by loose connective tissue with the exception of the veins at the cardia At this site the veins were rather strongly supported due to an increased thickness of the muscularis interna The mucosa was also more adherent in this region and was bound down to the sub mucosa by strong interlacing elastic fibers and connective tissue

(3) The coronary veins of the stomach in their ramifications pierce the muscular coats to reach the submucosa at the cardia At about this level occurs the transition from the absorbing epithelium to the pro tective epithelium Above this region in the cardia is the so called anas tomosis between the portal and caval circulation represented by small longitudinal venules with an absence of cross anastomosis for a dis tance of 3 to 4 cm Above this point the plexus is richly supplied with larger veins which anastomose freely in contradistinction to the struc tures at the cardia These veins then communicate by means of perfo rating branches with the larger periesophageal trunks to join the azygos and intercostal veins of the systemic circulation

(4) The lower part of the esophageal plexus therefore anastomoses with the upper part of the portal system at the cardia of the stomach through a system of extremely small venules It seems probable that in patients with portal hypertension this capillary like anastomosis at the cardia would offer marked resistence to the flow of blood from the portal system to the systemic veins Furthermore these findings offer no support to the theory that the recurrence of hematemesis can be pre

Portal Hypertension and Its Treatment

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CHRONIC portal hypertension results from a block in the portal system affording impedence to blood flow The syndrome of portal hypertension commonly known as Bantis syndrome is well known It consists of congestive splenomegaly secondary anemia leukopenia thrombocytopenia and a history of attacks of gastrointestinal bleeding or demonstrable evidence of the presence of esophageal varices Cases of portal hypertension may be classified in two groups depending upon the site of portal block (*1*) intrahepatic, for example due to cirrhosis of the liver and (*2*) extrahepatic, in which the liver is normal but there is a block in the portal vein itself or its radicals outside the liver The extrahepatic group represents approximately 30 per cent of the cases and in our experience the site of portal block is regularly confined to the portal vein itself the result of atresia thrombosis or cavernomatous transformation

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entirely alone and is surrounded by parenchyma throughout its course with the intervention of a small amount of perivascular connective tissue of the portal spaces There are no anastomoses either with the portal vein or the hepatic artery except through the sinusoidal bed and the two venous systems are always separated by parenchyma

There is an extraordinarily regular arrangement of the vascular terminals between the portal vein and the hepatic vein The central vein lies midway between any two corresponding portal terminals at a distance representing half of the so-called hepatic lobule Because of this the cell mass assumes a certain foliated or lobulated appearance Actually there is no definite separating fibrous tissue between the lobules each of the tiny masses of tissue so defined is continuous in man with the adjacent one by free sinusoidal and bile canalicular intercommunications and shows no trace of a fibrous capsule

Observing that the portal vein normally supplied 60 per cent of the hepatic blood flow and the hepatic artery but 40 per cent, McIndoe concluded that a balance of blood flow between the two systems was regulated by a delicate nervous mechanism derived from the splanchnics This mechanism located chiefly around the artery so regulates the high pressure arterial stream joining with the low pressure portal flow at the sinusoidal level as to reduce the pressure to a common level

Many of the conclusions concerning the circulation in the liver have been arrived at on the basis of indirect evidence obtained from perfusion and injection preparations of excised livers and from experimental ligation of the hepatic artery or portal vein

The recent perfection of a technic which permits direct observation of the distribution and manner of communication of the arterial portal and hepatic venous blood within the intact liver of living animals has done much to confirm and clarify some of our ideas concerning circulation in the liver Knisley (17) in 1939 was the first to use transillumination employing the quartz rod as a source of light He made direct microscopic observations of the intrahepatic circulation in the living animal (frog) He noted that the afferent hepatic arterioles and portal venules are contractile thus permitting the sinusoid to receive either mixed blood or blood from only one source He also noted a sphincter at the exit of each sinusoid which regulated the amount of whole blood or red cells contained in the sinusoid

Wakim and Mann (33) published a paper in 1942 which outlined improvements in Knisley's transillumination technic Employing the quartz rod with a constant temperature platform they reported exhaus

vented by the ligation or the excision of coronary veins the same can be said for periesophageal packing

CIRCULATION IN NORMAL LIVER

Some of the confusion and conflict of opinion regarding the effects of cirrhosis upon the circulation in the liver have been clarified in the light of a better understanding of the circulation in the normal liver

The liver consisting of a parenchyma within a freely expansible tissue framework has the unique circulatory feature of receiving a large volume of (portal) blood under low pressure and a smaller volume of (arterial) blood under high pressure with a common exit—the hepatic veins

The monumental work of McIndoe (18) portrays the anatomic arrangement and interconnections of the vascular systems of the normal liver as follows

(*1*) Portal vein Corrosion specimens of the portal vein show that it consists of a massive system of branches ascending directly without cross anastomosis through five or six successive orders of division to the sinusoidal circulation In general the branches are given off at right angles to the parent stem while the sinusoids themselves arise from the tips of the portal venules

(*2*) Arterial system The hepatic artery lies in close relationship to the portal vein within the portal space and occasionally winds around it Three groups of branches arise from the artery (*a*) Vaginal branches form an intricate arteriolar plexus in the connective tissue of *the portal spaces These are undoubtedly the main source of nourish*ment of the structures within the portal spaces They apparently end in capillaries which communicate with both the portal vein and the intercellular sinusoids (*b*) Vascular branches which end directly in the sinusoids at the periphery of the portal spaces (*c*) Capsular branches form an arteriolar anastomosis over the capsule These communicate with the phrenic internal mammary renal and suprarenal arteries

(*3*) Hepatic vein system A massive system of branches commencing at the central veins and passing through the sublobular veins to the inferior vena cava by five or six successive orders of division The central veins receive their tributary sinusoids from the parenchyma throughout their whole length unlike the portal veins which give off their sinusoids only from their extreme tips The hepatic vein runs

of the portal vein just before the latter empty into sinusoids at the periphery of the lobules

From these observations it is evident that the arterial blood supplying the hepatic parenchyma is by no means a negligible quantity nor is it ever justifiable to state that the hepatic artery supplies only the supporting tissue of the liver

(3) The normal liver has a great functional reserve in the activity of its vascular system the intrahepatic circulation manifests intermittent rhythmicity of irregular occurrence The whole circulatory condition of a single lobule or of several adjacent lobules may change from inactivity to partial activity and finally full activity when every sinusoid and even the oblique and transverse connections between sinusoids open up and blood rapidly flows through them into the central vein Comparing regions of circulatory inactivity with regions of activity at any one time it can be safely stated that more than 75 per cent of the regions showed inactivity when neither excitatory nor inhibitory factors were exercised over the intact liver

(4) The inactive sinusoids appear to go through two phases a storage phase during which the sinusoids are packed full of motionless blood cells and a nonstorage phase during which the sinusoids have scarcely any blood cells in their potential lumens

The storage phase may account in part for the very appreciable increase in the size of the liver that has been observed for example in dogs following the ingestion of food The least that can be said considering the many communications between the portal and arterial systems within the liver and the great variability of activity of the blood within the sinusoids is that the expansile tissue framework of the normal liver has little to do with maintaining a balance between the portal circulation and the hepatic artery circulation within the liver It seems highly probable that a delicate circulatory balance is mediated in this complicated circulatory system through a nerve or possibly a neurochemical mechanism such as postulated by McIndoe

Wakim and Mann have confirmed the above described distribution and manner of communication of the arterial portal and hepatic venous blood within the liver by employing two additional methods occlusion of vessels and the injection of dye Following occlusion of the hepatic artery for example a total cessation of blood flow invariably took place in the region under observation which was previously supposed and now is surely considered as independently supplied by arterial blood at the same time the portal sinusoids were practically

tive microscopic studies upon the intrahepatic circulation in both amphibian and mammalian livers

The direct observations made by the aforementioned investigators upon living functioning mammalian livers when taken together with McIndoe's work constitute the great pillars upon which rests our modern concept of the circulation in the human liver The distribution and manner of communication of the arterial portal and hepatic venous blood as directly observed is as follows

(1) The lobular configuration is fairly definite in the form of irregularly polygonal areas with a draining vein in their centers Upon higher magnifications it becomes evident that the hepatic artery and portal vein are seen more clearly in the periphery of the lobule and can be observed emptying into the sinusoids in a radial manner between columns of parenchymatous (liver) cells Very commonly long ramifications of the hepatic vein are located in the border of the liver receiving the sinusoids of that region and coursing parallel to the most peripheral edge of the liver to join the neighboring (hepatic) veins Frequently the portal branches with corresponding ramifications of the hepatic artery occupy such positions in the border of the liver and supply the sinusoids of the region with portal and arterial blood

(2) Distribution of venous and arterial blood At the borders of a lobule branches of the hepatic artery and portal vein break up into fine ramifications which usually empty independently into sinusoids both sets of which drain into the central vein Flow in the arterial sinusoids is comparatively much faster than that in the portal ones However cross communications have been observed between some neighboring arterial and portal sinusoids during their course to the central vein In addition to cross communication between arterial and portal sinusoids two other modes of communication are evident between the two kinds of blood

(a) Direct anastomotic communications are present between corresponding ramifications of the portal vein and the hepatic artery in their interlobular course Sometimes the arterial ramification ends at the anastomosis in the interlobular branch of the portal vein and no other arterial vessels are seen thereafter but the blood in the portal vein is observed to flow much faster immediately distal to the anastomosis In other regions there are transverse connections like the rungs of a ladder between the two vessels as they continue an independent course before they break up into several sinusoids at their termination

(b) Frequently arterial ramifications end in the terminal branches

(2) Interconnections at the sinusoidal level (*a*) Entrance of a terminal branch of the hepatic artery and a terminal branch of the portal vein into the same sinusoid (*b*) Cross communications between arterial and portal sinusoids

It has been demonstrated unequivocally that in the mammalian liver there are numerous sinusoids of the following varieties arterial sinusoids in which the entering vessel is a terminal branch of the hepatic artery portal sinusoids in which the entering vessel is a terminal branch of the portal vein and sinusoids containing mixed blood (portal and arterial) either as the result of terminal branches of both the portal and arterial systems entering the same sinusoid (as is often the case) or as the result of cross communications between portal and arterial sinusoids (as frequently occurs) in any case the vein of exit from the sinusoid is the central vein

The many types of communications that have been demonstrated to exist between the portal and arterial systems of the normal liver with the observed variability in their functional activity indicate an intricate relationship between the two circuits That this mechanism functions to guarantee adequate oxygen supply to the liver in case of serious alteration of the circulatory balance between the two circuits was well demonstrated by Schwiegk (28) This investigator observed that when the portal blood flow was decreased mechanically by compression of the portal vein the blood flow in the hepatic artery increased 50 to 100 *per cent In cirrhosis of the liver McIndoe demonstrated conclu*sively that the arterial circuit becomes a highly important compensatory factor serving to slow down the rate of destruction of liver cells in areas of maximum involvement and to promote regeneration of new areas of functioning liver tissue

McIndoe s contributions showing the effects of cirrhosis upon the liver and its circulation embraced a comprehensive and masterful study of the autopsy material from 16 patients Injections of gelatin containing India ink were made into the portal vein in situ injections of colored gelatin were employed for the arterial circuit Subsequently the corrosion method with wax reconstructions was carried out in 6 cirrhotic livers and several normal livers for comparative study The injection of colored gelatin was employed for a special study of the type of blood supply to independent nodules involved in the cirrhotic process A study of the collateral circulation in cirrhosis of the liver was made in particular respect to the intrahepatic network of collateral circuits Finally a method of perfusing the cirrhotic liver was carried out which

unaffected On the other hand occlusion of the portal vein led to cessation of flow in the totally portal sinusoids and left the arterial sinusoids unaffected In regions containing arteriovenous anastomoses between corresponding branches of the hepatic artery and the portal vein occlusion of the portal vein led to cessation of flow only in the region proximal to the arteriovenous anastomosis while the blood in the distal sinusoids kept moving It was noteworthy that the flow was reversed for a short distance in the portal vein proximal to the arteriovenous anastomosis *during the period of portal occlusion* However simultaneous occlusion of both hepatic artery and portal vein led to complete cessation of blood flow proximal and distal to the arteriovenous anastomosis and throughout the whole region under observation

STUDIES WITH INJECTION OF DYE

After identification of a region supplied by portal blood a 1 per cent solution of dye (methylene blue eosin Y Janus green B and so forth) in Ringer s solution was injected into the portal vein and the dye was detected in the sinusoids of the region under observation Then the portal vein was ligated and the blood containing the dye in the portal sinusoids topped flowing The microscope was shifted over a region supplied by arterial blood and a 1 per cent solution of India ink or a dye of color different from that used in the portal vein was injected into the external iliac vein It was observed repeatedly that the dye or ink particles appeared in the sinusoids supplied by arterial blood Under *low power magnification regions containing one dye* in the areas supplied with portal blood could be detected alternating irregularly with neighboring regions containing the other dye in the areas supplied by arterial blood These observations were confirmed by study of histologic sections from postmortem specimens of liver

The interconnections of the portal and arterial systems within the liver as demonstrated *anatomically* by McIndoe and *anatomically and* functionally by Wakim and Mann may be summarized as follows

(*1*) Interconnections at the presinusoidal level between ramifications of the arterial and portal branches in their course through the interlobular spaces (*a*) Direct side to side anastomosis between artery and vein (*b*) Transverse connections between artery and vein the two vessels thereafter continuing an independent course before breaking up into several sinusoids at their termination (*c*) Arterioles terminating end to side with portal venules

and has studied the intrahepatic collateral channels via which the portal blood is shunted before reaching the sinusoids of the parenchyma It has been proved that liver cells can get along without portal blood as such for example the many observations upon patients having complete extrahepatic portal block

Thus it may be safely said that the portal shunting phase of cirrhosis as just described which results in diversion of portal blood only does not seriously affect the nutrition of liver cells On the other hand in the course of the development of portal cirrhosis as the result of progressing fibrosis the disease enters a second phase which becomes most serious for the patient because of beginning interference with the arterial blood supply to the liver cells This may be referred to as the arterial shunting phase of the disease in which increasing resistance to arterial blood flow is encountered in the sinusoids as was so well demonstrated by McIndoe The resulting back pressure causes the arterial blood to flow through the many presinusoidal arteriovenous shunts directly into the portal circuit As more collateral veins are developed in response to the sharp rise in portal pressure due to the onset of arteriovenous shunting a greater and greater volume of arterial blood is shunted away from the liver cells A time thus comes in the advanced stages of the disease when all the portal blood and a great part of the arterial supply to the liver cells is by passed This means that the liver cells finally become almost completely starved because of the interposition of a low resistance arteriovenous portal-collateral circuit

The onset of the arterial shunting phase of cirrhosis marks the initiation of a vicious circle the future of which is simple to predict (1) complications from severe portal hypertension and (2) liver failure resulting from chronic anoxia

Herrick (15) in 1907 was the first to note the effect of arteriovenous shunting in advanced portal cirrhosis upon the pressure and flow in the portal circuit In arterial perfusion experiments upon excised normal and cirrhotic livers Herrick found that in the normal liver there is a rise in portal pressure of 1 mm of mercury for every 40 mm rise in arterial pressure whereas in the cirrhotic liver it was 1 mm for every 6 mm rise in arterial pressure Reversing the above experiments maintaining the arterial pressure at 130 mm of mercury it required only 10 mm of mercury to overcome arterial resistance to portal in flow in the normal liver compared to 40 mm of mercury in the cirrhotic liver Dock (10) confirmed Herrick s findings that in alcoholic

for the first time took into consideration and measured the amount of blood diverted through the collateral circuit

In comparisons of McIndoe s splendid specimens of injected cirrhotic livers with injected normal livers the most outstanding feature of the cirrhotic liver was the marked diminution of the total vascular bed *Both portal and hepatic* venous beds are equally affected and greatly reduced in size The main trunks are attenuated and irregularly stenosed The tiny portal veins are distorted twisted and curved upon themselves and finally break up into stunted venules from which irregularly scattered terminals arise The terminals of the portal and hepatic systems no longer alternate with one another but tend to lie together and assume a basketlike arrangement The central veins are pushed to the periphery of the lobule and finally lie next to the portal vein merged into the scar tissue which follows destruction of the liver cells Compression is seen within this scar tissue with slow obliteration of the smallest venous radicals by simple pressure atrophy the tendency *being toward the production of an avascular scar Hepatic* cells instead of being in a continuous sheet between the portal and hepatic venous trees are isolated to form innumerable irregular independent and anastomosing nodules Buried in dense fibrous tissue these nodules of liver cells are completely sidetracked from a supply of portal blood as has been demonstrated by the injection of colored gelatin The veins in these scarred areas are lost but the arteries persist as the injection of colored gelatin proved

EFFECTS OF CIRRHOSIS ON PARENCHYMAL BLOOD SUPPLY

In terms of our present concept of the hepatic circulation there is good evidence that in the early stages of a progressive cirrhosis the liver cells first begin to suffer from a lack of blood supply because of interference with blood flow through the easily compressible spongy intercellular sinusoidal spaces As has been demonstrated there are sinusoids receiving only portal blood others mixed portal and arterial *blood and finally sinusoids receiving only arterial blood* Therefore sinusoids carrying portal blood would be first affected in early cirrhotic changes because of their easy compressibility As fibrosis proceeds sinusoids carrying mixed arterial and portal blood would be next affected and finally portal blood would be totally excluded from the sinusoids and hence the liver cells McIndoe has successfully demonstrated the total *diversion of portal blood from the liver parenchyma*

in advanced cirrhosis as McIndoe s arterial perfusion experiments so well demonstrated even this source of nourishment becomes markedly impaired 40 to 45 per cent of the arterial perfusant by passes the liver parenchyma via presinusoidal arteriovenous anastomoses and flows into the portal collateral channels

The arteriovenous portal collateral circuit which becomes well established in advanced cases of cirrhosis of the liver is in effect no different from the arteriovenous varix or aneurysm which as is well known may seriously affect the nutrition of tissues by shunting arterial blood away from them

SURGICAL TREATMENT OF PORTAL HYPERTENSION

In the natural development of portal cirrhosis of the liver progress ing fibrosis so alters the circulation in the liver as to affect first the shunting of portal blood and as the disease advances the shunting of arterial blood In the portal shunting phase of the disease portal hyper tension is relatively benign with portal pressures varying from 15 mm of mercury (200 mm of water) to 25 mm of mercury (325 mm of water) In the arterial shunting phase of the disease however the portal hypertension becomes malignant the portal pressure often rising in excess of 45 mm of mercury (585 mm of water) In evaluating the results obtained from the various methods that have been recom mended for the treatment of portal hypertension it is essential that the above facts be kept in mind

For example even the slight reduction in portal pressure that is often effected by ligation of the splenic artery though it be transitory may serve to turn the tide of an ascites until restoration of proteins and electrolyte balance can be achieved under the favorable aegis of the modern medical regimen Such a result could be scored as a success for splenic artery ligation and thus promote its use for the treatment of portal hypertension But the facts are should the patient be followed that in the natural course of the disease there is the extreme likelihood of fibrosis progressing within the liver to the stage of arterial shunting with a marked rise in portal pressure

The many surgical procedures recommended for the treatment of portal hypertension may be grouped under the following headings

(1) Operations to effect an increase in portal outflow through collaterals Talma Morison operation (omentopexy)

(2) Operations to effect a reduction of portal bed arterial inflow (a) Ligation of splenic artery (b) Splenectomy

cirrhosis pressure "leaked" from hepatic arterial into portal venous system much more readily than in normal subjects

McIndoe in 1928 was the first investigator to make a complete study of the effects of cirrhosis upon the circulation of the liver Having demonstrated the presence of presinusoidal arteriovenous shunts and having noted the obstructive effects of fibrosis upon sinusoidal blood flow McIndoe made a careful study of the arteriovenous portal collateral circuit in advanced cirrhosis of the liver He perfused the portal vein or the hepatic artery with physiologic solution of sodium chloride at different pressures The time taken for a measured amount to pass through the liver was noted and the amounts returned from the hepatic vein and collateral channels were collected and measured

The results which McIndoe thus obtained were highly informative If in perfusing the portal vein he maintained a perfusion pressure varying from normal limits up to slightly portal hypertensive levels that is from 10 to 20 mm of mercury pressure 100 per cent of the perfusing fluid was collected from the collateral channels Even with the adjustment of the portal pressure to the moderately severe portal hypertensive level of 30 mm of mercury only 20 per cent of the fluid passed through the sinusoids to be collected from the hepatic veins 80 per cent of it by passed the parenchyma via the collateral circuit Finally though the portal pressure was raised to severe portal hypertensive levels for example 40 mm of mercury pressure only a relatively small amount of the perfusing fluid was collected from the hepatic veins (20 per cent) the rest being by passed through collateral channels

McIndoes experiments well demonstrated arterial shunting For example an arterial perfusing pressure ranging from a hypertensive level of 160 mm down to 80 mm of mercury resulted in the collection of 40 to 45 per cent of the perfusing fluid from the collateral channels This fluid by passed the parenchyma via presinusoidal arteriovenous anastomoses and passed into the portal collateral channels As little as 2 to 3 per cent of it was recovered from the portal vein the rest 50 to 53 per cent passed through the sinusoids and was collected from the hepatic veins

McIndoes studies clearly indicate that in advanced cirrhosis the portal blood never comes in contact with the hepatic parenchyma due to the presence of many intrahepatic collateral channels joining the portal vein before the sinusoidal bed is reached Liver cells therefore become entirely dependent upon arterial blood for their nutrition But

The question of an adequate immediate arterial blood supply to the spleen does not arise following ligation of the splenic artery in cases of portal hypertension This is because the short gastric arteries immediately take over Furthermore there are numerous anastomosing branches of the pancreatic artery that come in distal to the site of ligation of the splenic artery which rapidly expand as important collateral channels Actually the human spleen has practically a double arterial supply and following ligation of the splenic artery alone it is a matter of only a few months before there will be almost complete if not complete restitution of arterial blood flow to the spleen

It was only natural that ligation of the splenic artery should be tried for the control of portal hypertension It is a simple procedure easy to perform in conjunction with omentopexy Furthermore early estimates of the effect of splenic artery ligation upon portal blood flow were encouraging if misleading These estimates of reduction in portal blood flow following splenic artery ligation were based largely upon experimental data obtained immediately after splenic artery ligations in nonsurviving animals and varied from 20 to 40 per cent The estimates therefore bear no quantitative relationship with splenic artery ligation in man who relatively soon after operation is well on with the process of complete restitution of arterial blood flow to the spleen

There is of necessity a drop in volume flow and rate of blood flow in the spleen immediately following ligation of the splenic artery but even this probably varies in different cases since in many patients a partial or complete thrombosis of the splenic vein occurs

We have taken portal pressure readings at the operating table in a considerable number of patients before and after occlusion of the splenic artery The range of fall in portal pressure is from 5 mm to 25 mm of water On an experience embracing 157 cases of portal hypertension one of the outstanding observations was the wide variation in portal pressure readings obtained The lowest readings obtained were 240 mm of water the highest in excess of 600 mm and the average was 450 mm One observation was the consistent association of severe recurring gastrointestinal hemorrhage with the higher pressure levels In cases of cirrhosis of the liver having ascites alone the portal pressures usually ranged in the lower levels though unmistakable evidence of esophageal varices was present

In view of the foregoing ligation of the splenic artery for portal hypertension may be expected to yield apparent though often temporary success in patients with a slight rise in portal pressure above

(3) Operations to effect a reduction of blood flow through the esophageal varices (*a*) Ligation and excision of coronary veins (*b*) Transthoracic ligation and excision of periesophageal veins (*c*) Packing of the posterior mediastinum (*d*) Injection of the esophageal varices (*e*) Total or subtotal gastrectomy (*f*) Resection of the lower end of the esophagus with upper end of the stomach or the entire stomach

(4) Anastomoses between the portal venous system and the general systemic venous system (portacaval shunts)

Procedures to effect a potential increase in portal outflow via collateral channels embrace the apposition of tissues bearing portal blood with those whose venous drainage is into the caval system with the hope that additional collateral channels would result Sappey demonstrated the existence of veins running in the subperitoneal tissue lying between the folds of the hepatic ligaments connecting the portal trunk with the phrenic and azygos veins He described another large vein running in the round ligament and connecting the left branch of the portal vein with the epigastric and other veins in the abdominal parietes The coronary vein communicates with the azygos through the esophageal plexus And finally the inferior mesenteric vein communicates with the internal iliac by means of the middle and inferior hemorrhoidal plexuses

Talma Morison Operation The operation (31 11) presented the combined features of scarifying the peritoneal covering of the liver and spleen and the portions of parietal peritoneum opposed to them the encouragement of viscero parietal adhesions within the abdominal cavity and finally placing the great omentum in adhesive contact with the parietal peritoneum and the wound Though there have been modifications of the Talma Morison operation designed to improve its efficiency results have been most discouraging (8 14 21 22 23)

Operations to Reduce Portal Bed Arterial Inflow Of first consideration in the ligation of a large important artery is the maintenance of the tissue requirements of arterial blood in order to prevent immediate cell damage

Immediately following ligation of an important artery natures complicated mechanism for the development of collateral circulation is initiated It is natures law as first observed by John Hunter that finally after time has permitted the full development of collateral channels a complete restitution of blood flow will take place following ligation of a primary artery

The results appeared to be better in the individual case reports (which comprised most of the literature) than in the few instances of a series of several operated cases reported by the same author

The literature on splenectomy for portal hypertension (Banti s disease congestive splenomegaly splenic anemia) usually involved reports on a substantial number of cases the exact follow up results of which in the earlier reports are not always too clear (2, 19 20 24 34 37)

Barg and Dulin (2) in 1940 reported on 43 cases of Banti s disease comparing the results in 22 patients having splenectomy with 21 patients under medical treatment In the surgical group there were 6 postoperative deaths (27 per cent) The follow up results in 2 cases of the operated and in 4 cases of the unoperated series are not known leaving for comparison 14 cases of the operated and 17 cases of the unoperated series At the end of a 5 year follow up period 12 of the 14 patients in the operated series were dead (85 per cent) as against all 17 of the patients (100 per cent) in the unoperated series In respect to hematemesis in the splenectomized group 2 patients with a history of hematemesis continued to bleed postoperatively and 4 additional patients who were free of it before operation began having hematemesis following splenectomy In regard to ascites in cirrhosis cases 6 patients had ascites preoperatively only 1 of whom required repeated paracentesis postoperatively

Pemberton (24) in a review of 215 cases in which splenectomy was done for splenic anemia noted a high incidence (50 per cent) of recurrence of gastrointestinal bleeding following splenectomy Finally a quote from Whipple (37) thus summarizes the results For many years one of our most discouraging follow up problems in our Spleen Clinic at the Presbyterian Medical Center has been that of dealing with recurring hemorrhage in patients who had had a splenectomy for congestive splenomegaly or Banti s syndrome

OPERATIONS TO REDUCE BLOOD FLOW THROUGH ESOPHAGEAL VARICES Over the years procedures have been attempted which were intended to effect a reduction of blood flow through the esophageal varices No accurate evaluation of the effects of ligation or ligation and excision of the coronary veins the esophageal veins and so forth can be obtained from the literature Almost invariably such procedures were combined with splenectomy omentopexy or both with the desperate hope of preventing the recurrence of hemorrhage For example in the first case of coronary vein ligation reported (27) it became necessary to re operate and do a splenectomy because of recurrence of bleed

normal Usually portal hypertension in cirrhosis progresses in severity rather rapidly in contrast to portal hypertension due to extrahepatic portal block Splenic artery ligation alone is therefore out of consideration for the large cirrhotic group There is the occasional patient no doubt a victim of persistent hemorrhage and in bad condition for whom splenic artery ligation may be considered with the chance of temporary relief to afford an opportunity for the successful establishment of a portacaval shunt However even in these cases preparation for successful shunting can usually be accomplished satisfactorily by transfusions together with esophageal balloon tamponage combined with frequent feedings via the nasogastric tube

Splenic artery ligation has a better chance of a more prolonged success in cases having slight portal hypertension belonging to the extrahepatic portal block group We hasten to state emphatically however that the disease is progressive if slowly even in this group and splenic artery ligation or splenectomy should not be done because (1) as previously explained portal hypertension if somewhat reduced at first is not permanently relieved by such procedures and (2) of more importance ligation of the splenic artery (with its attendant high incidence of splenic vein thrombosis) or splenectomy render the splenic vein unfit for direct anastomosis with the left renal vein at any subsequent date

In cases of portal hypertension due to extrahepatic block the site of block is regularly in the portal vein itself thus rendering it unfit for shunting purposes This leaves the splenic vein as the one best vein for shunting procedures in the extrahepatic portal block group Ill advised splenectomies or splenic artery ligations therefore deprive these patients of the one great opportunity of obtaining permanent relief from the threat of death from hemorrhage

Happily however there is new hope for the "postsplenectomy bleeder A technic and apparatus for continuous regional heparinization for postoperative use (7) offers great promise of success with vein grafts to establish intra abdominal venous shunts Follow up observations on patients who have had the advantages of these improved technics are now slightly over a year So far the results are most encouraging All the patients are alive but some have had a return of hemorrhage A substantial fall in portal pressure to a figure well below hemorrhage levels often follows opening of these vein graft shunts

Little positive information was gleaned from a review of the literature on splenic artery ligation for portal hypertension (1 4 5 6 13 36)

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The literature on splenectomy for portal hypertension (Banti s disease congestive splenomegaly splenic anemia) usually involved reports on a substantial number of cases the exact follow up results of which in the earlier reports are not always too clear (2, 19 20 24 34 37)

Barg and Duhn (2) in 1940 reported on 43 cases of Banti s disease comparing the results in 22 patients having splenectomy with 21 patients under medical treatment In the surgical group there were 6 postoperative deaths (27 per cent) The follow up results in 2 cases of the operated and in 4 cases of the unoperated series are not known leaving for comparison 14 cases of the operated and 17 cases of the unoperated series At the end of a 5 year follow up period 12 of the 14 patients in the operated series were dead (85 per cent) as against all 17 of the patients (100 per cent) in the unoperated series In respect to hematemesis in the splenectomized group 2 patients with a history of hematemesis continued to bleed postoperatively and 4 additional patients who were free of it before operation began having hematemesis following splenectomy In regard to ascites in cirrhosis cases 6 patients had ascites preoperatively only 1 of whom required repeated paracentesis postoperatively

Pemberton (24) in a review of 215 cases in which splenectomy was done for splenic anemia noted a high incidence (50 per cent) of recurrence of gastrointestinal bleeding following splenectomy Finally a quote from Whipple (37) thus summarizes the results For many years one of our most discouraging follow up problems in our Spleen Clinic at the Presbyterian Medical Center has been that of dealing with recurring hemorrhage in patients who had had a splenectomy for congestive splenomegaly or Banti s syndrome"

OPERATIONS TO REDUCE BLOOD FLOW THROUGH ESOPHAGEAL VARICES

Over the years procedures have been attempted which were intended to effect a reduction of blood flow through the esophageal varices No accurate evaluation of the effects of ligation or ligation and excision of the coronary veins the esophageal veins and so forth can be obtained from the literature Almost invariably such procedures were combined with splenectomy omentopexy or both with the desperate hope of preventing the recurrence of hemorrhage For example in the first case of coronary vein ligation reported (27) it became necessary to re operate and do a splenectomy because of recurrence of bleed

ing 6 weeks after ligation I myself witnessed an operation done through a thoracoabdominal approach embracing the most radical ligation and excision of the coronary and the periesophageal systems of veins followed by splenectomy in an 8 year old boy having portal hypertension secondary to extrahepatic portal block Within 6 months the child had severe hematemesis Walters *et al* (34) in 1940 presented the results obtained at Mayo Clinic from the various procedures for the control of bleeding from esophageal varices There were 9 patients who had undergone ligation of the coronary veins and splenectomy 6 of them had recurrence of bleeding 1 patient was lost to follow up Of 3 patients having coronary vein ligation splenectomy and omentopexy two had recurrence of bleeding postoperatively

In 1939 Crafoord and Frenckner (9) introduced the injection treatment for esophageal varices reporting 1 case with a successful outcome 3 years following treatment As would be expected this method has been faithfully tried over the years and the over all results have been so poor that it has been largely abandoned

In 1947 Som and Garlock (30) reported 2 patients with portal hypertension in whom gauze packing was introduced via the posterior mediastinum and left for a time in contact with the esophagus They stated that the patients had been free from hemorrhage for 6 years and 14 months respectively since operation In our series of 8 patients in whom this method was employed all had a return of hematemesis within 12 months postoperatively

In 1945 Wangensteen (35) advanced the hypothesis that an ulcer diathesis existed in patients having portal hypertension which disposed them to the occurrence of hematemesis the result of acid peptic digestion The evidence for this was derived from experiments upon rabbits and dogs in which he was able to show that histamine provoked ulcers occurred more readily in those stomachs in which there was obstruction to venous drainage Preliminary experiments on dogs suggested definitely that a 90 per cent resection of the stomach afforded real but not absolute protection against histamine provoked ulcer in the presence of portal hypertension He reported 4 patients having portal hypertension with esophageal varices in whom extensive (90 per cent) gastric resections had been done The longest follow up period in these cases was a few months

Baronofsky (3) in 1949 reported on Wangensteen s series of cases Extensive (90 per cent) gastric resections had been performed in 8 patients with portal hypertension 4 patients 3 of whom had impaired

liver function (cirrhosis) died postoperatively Of the remaining 4 1 died of hemorrhage and 3 were reported as doing well the longest follow up period being 2 years

In 1947 Phemister and Humphreys (25) advanced the idea of abolishing the coronary esophageal circuit of collateral veins by doing a total gastrectomy and resection of the esophagus with restoration of continuity by means of a jejunal anastomosis with the proximal end of the esophagus They thought that this extensive procedure might prove lifesaving for that unfortunate group of postsplenectomy bleeders with normal livers in whom the site of portal block was extrahepatic and all other measures had failed

They reported 2 case belonging in the above category in which this extensive procedure had been carried out without mishap The first case had been followed 2 years and 8 months during which time there had been one moderate and one slight bleeding episode In the second case the follow up period had been only 3½ months

One obvious defect of this procedure is that it again brings the high pressure portal system in anastomotic junction with the low pressure caval system of veins But in the circumstances in which it is advocated the procedure is justifiable and may be lifesaving Phemister in an unpublished report stated that none of his patients who had undergone operation had died While approximately 50 per cent of them had had hemorrhages since operation the hemorrhages tended to become less severe with the passage of time Certainly the high incidence of hemorrhage following this procedure in which the entire stomach is removed lends little support to the concept of acid peptic digestion as the causal factor in hemorrhage

Portacaval Shunt for Relief of Portal Hypertension

The most rational and physiologic way of reducing an increased portal pressure (portal hypertension) is by the establishment of a portacaval shunt that is the anastomosis of the portal vein or one of its major radicals to the vena cava or one of its major radicals for example the renal vein Eck (12) in 1877 was the first to anastomose the portal vein to the vena cava in dogs for experimental purposes and suggested its use for the correction of portal hypertension Vidal (32) in 1903 performed the operation successfully in a case of cirrhosis with relief of ascites In the next decade several cases were reported

ing 6 weeks after ligation I myself witnessed an operation done through a thoracoabdominal approach embracing the most radical ligation and excision of the coronary and the periesophageal systems of veins followed by splenectomy in an 8 year old boy having portal hypertension secondary to extrahepatic portal block Within 6 months the child had severe hematemesis Walters *et al* (34) in 1940 presented the results obtained at Mayo Clinic from the various procedures for the control of bleeding from esophageal varices There were 9 patients who had undergone ligation of the coronary veins and splenectomy 6 of them had recurrence of bleeding 1 patient was lost to follow up Of 3 patients having coronary vein ligation splenectomy and omentopexy two had recurrence of bleeding postoperatively

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renal vein In view of the fact that the portal vein itself is regularly the site of block in these cases thus rendering it unfit for shunting purposes we were forced to employ veins of inadequate size for example the mesenteric veins in establishing the shunts Because of this there was a high failure rate in our early attempts to salvage these postsplenectomy bleeders But with the coming of a method of continuous regional heparinization for postoperative use which insures success with the employment of vein grafts our percentage of salvage has greatly increased in this unfortunate group

We began to realize after a time that the nonsuture method employing vitallium tubes for venous shunts had an undesirably high failure rate and we shifted to anastomosis by suture exclusively In 14 patients having direct suture anastomosis of the splenic vein end to side with the left renal vein there was a single failure

Follow up on 90 cases of cirrhosis of the liver having portacaval shunts ranges from 2 months to 6 years There have been 17 deaths as follows

(*1*) There were 6 deaths from hemorrhage roughly a 6 6 per cent failure for the shunting procedure In 4 of the 6 failures the ill fated vitallium tube was used in establishing the shunt The anastomoses were of the splenorenal variety in 5 of the 6 failures

(2) Liver failure was the cause of death in 7 patients (7 7 per cent) all belonging to the Group II series who at the time of operation had severely damaged livers It is of interest to note however that 4 of these patients worked until a short time before death They lived for 4 3 2 and 1 year respectively following operation

(3) The cause of death in the 4 patients who died of other causes was pneumonia and embolism 1 case ruptured peptic ulcer 1 case nephritis 1 case and leukemia 1 case

Of the 73 patients living 58 are active and working In 7 patients activity is still restricted but in 4 of these there is evidence of improvement of the liver Among the 73 patients being followed there is 1 patient who has had a minor attack of gastrointestinal bleeding Many patients have shown amazing clinical improvement and improvement in the functional status of the liver

Evidence has accumulated which indicates that the primary role of the portacaval shunt is first to protect patients from untimely death due to hemorrhage and second to protect livers of cirrhotic patients from the deleterious effects of recurring hemorrhage and wasting ascites thus affording an opportunity for healing and regeneration of

The successful establishment of portacaval shunts awaited the modern era of surgery With the coming of control of infection and shock better anesthesia and improved surgical management it was natural that portacaval shunting should profit as has all vascular surgery from these advances The portacaval shunt may now be accomplished at a reasonable risk

In our series of 42 cases of portal hypertension due to extrahepatic portal block there were 3 postoperative deaths (7 1 per cent) In 115 cases of cirrhosis of the liver the mortality was 21 7 per cent Classifying these cirrhosis cases on the basis of severity of liver damage there were 61 patients classified as Group I, or good risk patients The postoperative mortality in this group of 61 cases was 11 4 per cent In 54 cases in Group II those having evidence of severely damaged livers the mortality rate was 33 per cent The latter group was made up for the most part of neglected patients with evidence of long standing severe portal hypertension This group is already diminishing in numbers because patients are being referred soon after the onset of unmistakable evidence of severe portal hypertension for evaluation for shunting procedures It is only a matter of time when the number of cases in Group II will be decidedly small in comparison with those in Group I Even so in this series of 115 cases of cirrhosis operation was accomplished in over half (61 cases) at a comparatively low risk (11 4 per cent) Add the 61 cases to the 42 cases of portal hypertension due to extrahepatic block and it makes 103 cases or 65 6 per cent of the entire series of 157 cases The postoperative mortality rate in these 103 cases was 9 7 per cent which means that approximately two thirds of the patients with portal hypertension are remarkably good risks for the shunting procedure The mortality rate for the entire series of 157 cases including 54 cirrhosis cases that were an exceedingly poor risk was 17 8 per cent

During the development of our series we have particularly concentrated upon ways and means of minimizing operative risk for once a portacaval shunt is established employing either the portal or splenic vein the chances of these patients remaining free from attacks of hemorrhage are excellent Only 1 patient having a portal vein to vena cava anastomosis has died of recurring hemorrhage and in this patient a fairly recent partial (40 per cent) thrombosis of the portal vein was noted at the time of operation Of the 42 patients with extrahepatic portal block 40 per cent had had their spleens removed thereby rendering the splenic vein unfit for direct anastomosis with the left

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liver parenchyma under the favorable influence of modern medical management

The portacaval shunt affects portal pressure directly in accordance with the size of the shunt This important feature gives control of portal pressure as determined by direct measurement and serves to confine the effect where it is desired—in the portal vein and its radicals This direct means of control is of great importance when dealing with cirrhosis of the liver as was so well emphasized by McIndoe in 1928 from whom I quote the following

> It seems safe to conclude that in advanced cases of cirrhosis the liver is virtually in the condition of having an Eck fistula between the portal vein and the vena cava and that the task of sufficient blood to the parenchyma for normal metabolism is relegated to the hepatic artery When even this mechanism fails the patient dies from hepatic insufficiency due to insufficient blood supply to the parenchyma rather than to an actual deficiency in the amount of hepatic tissue From the experiments of Mann and his associates it is certain that an exceedingly small amount of hepatic tissue properly nourished is required for normal metabolism much less in fact than is present in the most advanced cases Considering that the whole tendency of portal cirrhosis is to divert the portal blood stream away from the liver leaving the arterial blood to provide for the parenchymal requirements the most logical and effective method of dealing radically with the embarrassed portal circulation would doubtless be to perform a simple Eck fistula By this means the portal hypertension would be relieved stasis immediately abolished and the development of varices arrested

Our discussions to this point have served to emphasize the fact that the mechanism of origin of portal hypertension in liver cirrhosis is vastly more complicated than extrahepatic portal block

With improved methods of studying the volume of blood flow through the liver it is hoped that in the near future further information will be forthcoming At the present time Dr Stanley Bradley is collaborating in a study of the volume of blood flow in cirrhotic livers before and after shunting The number of patients studied is as yet small—too small from which to draw any final conclusions but some interesting points have already been established (*1*) Estimated hepatic blood flow is below normal in cirrhosis (*2*) With the establishment of portacaval shunts there is a further decrease in blood flow but an increase in oxygen extraction and bromsulfalein extraction

There has so far been considerable variability of the blood flow changes in different cases of cirrhosis It is hoped that in time this may be correlated in a significant way with portal pressure in respect to the portal shunting and arterial shunting phases of the disease

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The Anemia of Infection

XVII A Review*

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INTRODUCTION

PROFOUND metabolic alterations take place in man during infection Scarcely any system escapes some change in its function It is therefore not surprising that the functional capacity of the erythron should be altered as well

That this is true was evidently appreciated by Andral and Gavarret (3) as early as 1842 These workers drew blood into two containers The blood in one container was allowed to coagulate and the blood in the other container was stirred and the fibrin removed The fibrin the red cell clot and the solid ingredients of the plasma were then weighed and the values expressed in parts per 1 000 parts of whole blood In certain patients with infections such as erysipelas acute inflammatory rheumatism and phthisis they found the red cell mass to be reduced from a normal of 110 to 140 to 40 to 50 parts per 1 000 parts of whole blood In typhus fever and in smallpox the red cell mass was reduced to a lesser degree while in measles no reduction was observed

These observations were later confirmed by Andral (2) and by

* The work described in this paper was commenced under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Utah The expenses of these investigations were subsequently defrayed by grants from the United States Public Health Service and in part by Parke Davis and Company Detroit Michigan, and the Upjohn Company Kalamazoo Michigan

Becquerel and Rodier (9) Sorenson (144) in 1877 by the use of the newly developed technic of direct counting of red cells observed that there were fewer cells in pneumonia and rheumatic fever Laache (80) in 1883 by the use of Malassez s counting method and hemoglobinometer observed lowered red cell and hemoglobin values in tuberculosis syphilis and typhus fever Hayem (61) in 1889 discussed the anemia associated with various infections in some detail The more recent contributions of Naegeli (105) Heilmeyer and associates (62 63) Thoenes and Aschafferburg (147) Schaefer (124–131) in Germany Vannotti and co workers (151–153) and Hemmeler (64) in Switzerland and Valquist (150) and Nilsson (107) in Sweden and Vaughan (155 156) in England have greatly extended our knowledge of this type of anemia Our own laboratory has been engaged in the study of this problem since 1944 (24–29 31 48 49 51 54 55 59 79 93 171–173)

It is the purpose of this presentation to summarize correlate and interpret our own observations The work of others pertaining to this topic especially when their work offers additional information rather than similar observations will be reviewed in some detail in order to give a more complete description of the anemia of infection Otherwise the studies will be simply mentioned as they are pertinent to the topic under discussion Reference will be made to experimental studies in animals and the possible significance of these investigations in relation to the anemia in man will be considered Other types of simple chronic anemia will be compared with the anemia associated with chronic infections and an effort will be made to correlate the metabolic changes more obviously related to the anemia with a few of the many other metabolic changes which occur with infections Reference will be made also to the rather large gaps in our knowledge of this anemia which still exist

✓ DEFINITION Anemia may develop in association with infections in several different ways Very occasionally the infection may lead to blood loss and consequently to anemia Rarely through some process as yet poorly understood the infection may be associated with well marked signs of hemolytic anemia or the infection may accentuate a pre existing unrelated anemia such as iron deficiency anemia or pernicious anemia However much more commonly anemia develops during the course of the infection without evidence of blood loss or the usual clinical evidences of hemolysis This is what we consider the "anemia of infection and it is with this anemia that this paper is specifically concerned

INCIDENCE The anemia associated with infection is one of the most commonly encountered forms of anemia if not the most common of all Sturgis (145) in a survey of 1 459 patients with anemia admitted to the University of Michigan Hospital found "simple chronic anemia" in 59 per cent In approximately 95 per cent the anemia developed in association with a chronic infection Baty (7) in a study of the etiologic factors in 514 cases of anemia in infants and children classified infection as the etiologic factor in 49 per cent From an analysis of 3 000 cases of anemia in infants and children Diamond (37) concluded that in 61 per cent the anemia was secondary to an infection

With the newer means for controlling infections it may be anticipated that the incidence of the anemia of infection will be greatly reduced Already the incidence of such diseases as empyema lung abscess and chronic osteomyelitis has been lowered significantly

FACTORS AFFECTING DEVELOPMENT OF ANEMIA

The factors which determine whether or not anemia will develop in a patient with an infection deserve careful analysis

TYPE OF INFECTION Anemia is frequently associated with such infections as empyema lung abscess bronchiectasis chronic osteomyelitis pneumonia subacute bacterial endocarditis chronic urinary tract infections pelvic inflammatory disease tuberculosis brucellosis meningococcemia cellulitis and chronic fungus infections (28 64 122, 145) In our series of 50 selected patients with anemia due to an infection the primary diagnoses were as follows empyema 10 patients chronic osteomyelitis 8 pneumococcal pneumonia 6 subacute bacterial endocarditis 5 tuberculosis 5 lung abscess 4 cellulitis 4 actinomycosis 3 and miscellaneous 5 Except in tuberculosis data concerning the frequency of anemia in association with each of these infections are not available The *incidence of anemia in tuberculosis* has been reported to be approximately 20 per cent (12 102)

No information is available whether the location of the infection (in bones lungs liver subcutaneous tissue or elsewhere) is of any importance in the development of the anemia Whether one type of organism e g streptococcus pneumococcus aerobacter is more likely to produce anemia than another is not known James *et al* (73) in a study of patients with various suppurative lesions presented evidence that in those patients whose infections were due to several different organisms there was a correlation between the hemoglobin levels and

the number of different varieties of organism in the wound The greater the number of different genera of organisms the lower were the hemoglobin levels

SEVERITY OF INFECTION It is our impression that the severity of the infection as indicated by the severity of the accompanying systemic reaction is probably the most important factor in determining whether or not anemia will develop provided the infection persists for a sufficiently long period of time Infections of mild degree are generally not accompanied by anemia James *et al* (73) in a study of 87 patients with chronic infections classified 72 as moderately severe and 15 as severe This classification was based on the degree of fever leukocytosis suppuration and exudation The incidence of anemia in these two groups was 10 per cent and 40 per cent respectively The incidence of anemia in the entire group was 15 per cent

DURATION OF INFECTION *Infections of less than a month s duration* as a rule are not accompanied by significant anemia Since the normal life span of erythrocytes is approximately 4 months this would be expected if it is admitted that the anemia is due to decreased production of erythrocytes by the bone marrow In our series of 50 patients all had had an active infection for at least 1 month The average duration of the infection for the entire group was approximately 5 months We have not observed significant anemia in patients with infections of less than 1 month s duration The longer the duration of the infection the more likely is anemia to develop

AGE OF PATIENT The anemia of infection occurs commonly in infants and children (7 37) In our series of 50 adult patients the age distribution was as follows 10 to 19 years 5 patients 20 to 29 years 7 30 to 39 years 6 40 to 49 10 50 to 59 10 60 to 69 7 70 to 79 4 and 80 to 89 1 From these limited data it would seem that no age group is spared and that age is not an important determinant except perhaps as regards resistance to infection

PREVIOUS NUTRITIONAL STATUS The previous nutritional status of the patient may possibly be of some importance in determining whether or not *anemia develops it is generally assumed that more severe* and prolonged infections are likely to develop in inadequately nourished individuals It is plausible that nutritional inadequacy may impair the functional capacity of the bone marrow (22) However observations concerning the incidence and severity of anemia in a significant number of individuals with various types of infections and in relation to their nutritional status are lacking

SEVERITY OF ANEMIA

The anemia associated with chronic infection as indicated by the quantity of hemoglobin per unit volume of blood is generally mild in degree Occasionally it may be moderately severe and only rarely if ever is it pronounced Indeed a severe anemia is so rare

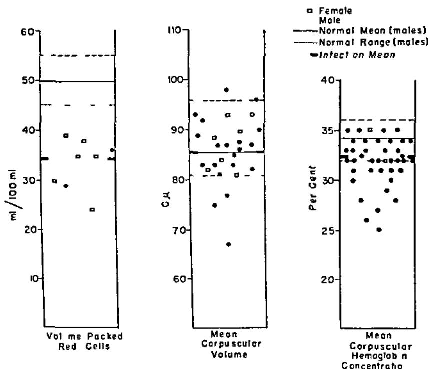


Fig 1 —Volume of packed red cell mean corpuscular volume and mean corpuscular hemoglobin concentration of the erythrocytes in 50 patients with anemia of infection

that its presence should make one suspect the presence of another cause for anemia such as renal disease iron deficiency or increased blood destruction

The severity of the anemia in our series of 50 patients is indicated in Table I and Figure 1 The most severe degree of anemia was observed in association with lung abscess (mean value for volume of packed red cells (V P R C) 27 8 ml /100 ml) and the least anemia

was found in association with pneumonia (mean V. P. R. C. 36.8 ml./100 ml.). Between these extremes in order of decreasing anemia were subacute bacterial endocarditis, tuberculosis, empyema and chronic osteomyelitis.

The severity of the anemia was correlated not only with the severity of the infection but also, within limits, with the duration of the infection. Anemia rarely appears before 1 month; over the next several months the anemia slowly but progressively becomes more severe and thereafter remains relatively constant. In our series the mean value for volume of packed red cells for 20 patients with infections of 1 to 2 months duration was 36 ml. per 100 ml., whereas the mean

TABLE I

Severity of the Anemia in 50 Patients with Chronic Infections

Vol. Packed Red Cells Ml./100 Ml.	Patients
35-39	29 (58%)
30-34	12 (24%)
25-29	8 (16%)
20-24	1 (2%)

value for 7 patients with infections of 6 to 11 months duration was 33. In 10 patients infection had been present for a period greater than 12 months and in these the anemia was no greater in degree than in those with infections of 6 months duration.

In this regard Hemmeler (64) has made some noteworthy observations. In a careful study of 25 patients with chronic infections he found that at the onset of an infection the percentage of reticulocytes in the peripheral blood was essentially normal. As the infection progressed the reticulocytes decreased and thereafter anemia slowly developed. He has termed this the "aplastic phase." If then the infection subsided reticulocytes reappeared and blood regeneration took place. If, however, the infection persisted, the scarcity of reticulocytes continued and the anemia progressed in severity. But at a certain point and without clinical improvement, reticulocytosis took place spontaneously and there was an interruption in the declining red cell or hemoglobin curves. During this phase of regeneration the anemia either became somewhat less marked or, if the reticulocytosis was not great, the anemia remained constant in degree and no longer increased in severity.

Thus it would appear that when a certain degree of anemia is reached the inhibition of erythropoiesis is relieved to such an extent

as to allow a balance to be reached between the rates of red cell production and the senescence of these corpuscles The level at which the reticulocytosis develops varies In Hemmeler s cases this generally occurred when the hemoglobin decreased to about 60 per cent of normal

The true severity of the anemia may not be revealed by studies of the quantity of hemoglobin per unit volume of blood since it has been *suggested that the total blood volume may be markedly reduced in patients* with chronic sepsis Lyons (92) in a study of 5 patients with chronically infected gun shot fractures found that the hemoglobin per 100 ml blood was reduced only 24 per cent below the normal mean of 15 Gm per 100 ml whereas the total circulating hemoglobin was reduced approximately 50 per cent below the normal values calculated according to the weight of the patients prior to injury In a more recent study of 28 patients with chronic infection Lyons *et al* (32) found that the blood volume was reduced to 76 per cent of normal as judged by the weight of the patient prior to illness whereas the total circulating hemoglobin ranged from 50 to 66 per cent of the standard calculated value The average total plasma volume was 92 per cent of the calculated normal The degree of reduction in hemoglobin per unit volume of blood was not given for this group of patients

In 138 of 145 patients with various diseases including chronic sepsis malignancy and malnutrition from various causes Nelson *et al* (106) also observed a considerably greater reduction in total circulating hemoglobin than in hemoglobin per unit volume of blood Gregersen (50) in referring to patients with chronic wound infections stated that "the hematocrit value and the plasma protein concentration may remain essentially normal and give no indication of the large deficiency in blood volume In this article no supporting data were presented

The results of blood volume studies in 10 male patients in our series (115) are presented in Table II

Plasma volume determinations were made by the Evans blue (T 1824) method The total blood volume was then calculated from the corrected hematocrit value and the total circulating hemoglobin in grams was obtained by multiplying the hemoglobin in grams per 100 ml by the blood volume in milliliters divided by 100 The estimated normal total circulating hemoglobin for each individual was calculated by assuming a normal hemoglobin of 17 Gm per 100 ml and a blood volume of 85 ml per kilogram of body weight (weight prior to illness) The average decrease in hemoglobin in the 10 patients

TABLE II

TOTAL CIRCULATING HEMOGLOBIN (T C H) IN 10 PATIENTS WITH CHRONIC INFECTIONS

Patient	Before Illness		During Illness					During Recovery				
	Body Weight kg	Estimated Normal T C H Gm	Body Weight kg	Hemoglobin Gm %	Hemoglobin % Dec	T C H Gm	T C H % Dec	Body Weight kg	Hemoglobin Gm %	Hemoglobin % Inc	T C H Gm	T C H % I
F M	52 2	755	40 9	11 7	31	420	44	47 7	14 1	20	545	28
K J	66 4	957	62 3	12 4	27	500	48	63 5	13 6	10	564	13
F T	50 8	735	56 1	12 3	28	490	33	50 8	14 7	19	750	50
J B	63 6	920	47 3	11 3	34	496	46	53 4	15 3	35	750	51
D S	69 5	1005	63 6	12 3	28	620	38	69 2	15 1	23	747	21
T C	63 6	920	52 3	9 6	43	468	49					
W B	72 6	1050	63 2	11 4	33	532	48					
I L	63 6	920	53 7	9 7	43	433	53					
I I	48 2	695	42 7	11 3	34	445	36					
J R	56 3	814	50 1	14 1	17	541	34					
Mean	*60 7*	*877*	*53 2*	*11 6*	*32*	*495*	*43*	*56 7*	*14 7*	*21*	*667*	*33*

Plasma volume (P V) determined with T 1824

Blood volume $= \frac{PV \times 100}{100 - (VPRC \times 0.915)}$

T C H $= \frac{Hb (Gm \%) \times \text{Blood volume (ml)}}{100}$

Estimated normal T C H calculated by using normal hemoglobin of 17 Gm per 100 ml of 85 ml per kg of body weight

as indicated by the quantity per 100 ml of blood was 32 per cent whereas the decrease in total circulating hemoglobin was 43 per cent That these calculations are reasonably valid is suggested by the fact that in the 5 patients followed until recovery the hemoglobin increased 33 per cent as calculated from the total circulating hemoglobin whereas the increase in hemoglobin in grams per 100 ml was 21 per cent

The above studies nevertheless are not conclusive and are open to several criticisms Certain errors are encountered in calculating the total blood volume from the plasma volume as determined by the Evans blue method Since there is a wide range for normal blood volume it is exceedingly difficult to estimate accurately the "normal blood volume" for a particular patient Whether the "normal" blood volume should be calculated on the basis of the weight of the patient prior to the illness or in accordance with his weight during the illness can be debated In support of the first method Clark *et al* (32) have presented a limited amount of data indicating that *if the total blood volume is restored by transfusions to the standard volume assigned on the basis of the weight of the patient in health* the values for total circulating hemoglobin and total red cell mass are maintained at this level

It is obviously desirable that simultaneously with the Evans blue plasma volume measurements the total red cell mass be determined with P^{32} labeled red cells Such studies should also be made in the *same patient during the period of infection and again after complete recovery* This information is now being gathered in our laboratory

MORPHOLOGIC CHARACTERISTICS

The anemia associated with chronic infection is usually normocytic and normochromic (28 64) It may occasionally be slightly microcytic and hypochromic In our series of 50 patients the average mean corpuscular volume (M C V) for the group was 86±6.2 c μ The average mean corpuscular hemoglobin concentration was 32±2 6 per cent (Table III) In 5 patients the mean corpuscular volume was less than 80 c μ and in 7 the mean corpuscular hemoglobin concentration was less than 30 per cent (Fig 1) Microcytosis when present was not marked except in 1 patient This individual had osteomyelitis of 3 years duration and was not deficient in iron as indicated by failure to respond to either oral or parenteral iron therapy

One of us (169) in a study a number of years ago of 18 cases of

inflammatory disease which included pneumonia pulmonary abscess chronic cholecystitis chronic arthritis and infections of the genito urinary tract found an average mean corpuscular volume of 87 c μ and an average mean corpuscular hemoglobin concentration of 34 per cent In 27 other cases of similar character the anemia was somewhat micro cytic (M C V 72 to 65 c μ) but not hypochromic (31 to 34 per cent)

TABLE III

MORPHOLOGIC AND CHEMICAL CHARACTERISTICS OF ANEMIA OF INFECTION

Determination	Normal			Infection†		
	No	Mean ± S D	Range	N	Mean ± S D	Range
Volume packed red cells ml /100 ml	30	50 ± 2 3	44–55	50	34 ± 4 3	26– 40
Mean corpuscular volume c μ	30	86 ± 4 9	81–96	50	86 ± 6 2	67– 98
Mean corpuscular hemoglobin conc %	30	34 ± 1 0	32– 36	50	32 ± 2 6	25– 36
Plasma iron μg /100 ml	50	105 ± 30 3	43–210	50	30 ± 9 1	14– 64
Total iron binding capacity of serum μg /100 ml	15	347 ± 26 1	306–396	13	195 ± 54 5	80–269
Plasma copper μg /100 ml	52	114 ± 15 5	86–161	36	197 ± 43 1	126–267
Whole blood copper μg /100 ml	32	93 ± 11 1	69–117	24	139 ± 19 2	106–190
Free erythrocyte protoporphyrin μg /100 ml	33	32	13– 79	35	180	36–634
Total urinary coproporphyrin μg /24 hr	22	106 ± 23 1	40–150	14	275	145–550

M l
†43 mal s 7 fe al Fl f l g o p d d not d ff g fi tly from the male g o p ny f the det rm t o
Sk w d t but n

Of 464 cases of anemia studied in no instance was macrocytic or hypo chromic anemia observed in association with infection uncomplicated by blood loss or nutritional deficiency Thus the anemia of infection was classified as normocytic or simple microcytic in type

Saifi and Vaughan (122) in a study of various acute and chronic infections such as osteomyelitis chronic meningococcemia cellulitis empyema subacute bacterial endocarditis and chronic pyelonephritis found normocytic anemia in 11 cases and obtained microcytic indices in 4 patients The color index varied from 0 53 to 0 95 but in the ma jority it was above 0 8 The lowest values for the color index were ob served in the patients with infections of longest duration Frequent reference especially in the earlier literature is made to a reduction

in the color index in infections (35 70 77 110) This as indicated above is usually more or less equivalent to the degree of decrease in cell size James *et al* (73) noted a very slight diminution in the mean corpuscular hemoglobin concentration in prolonged infections

In a detailed study of 250 patients with tuberculosis and anemia Muller (102) observed macrocytic anemia in 12 per cent The macrocytic anemia in most instances was associated with severe hemorrhage and reticulocytosis The patients with microcytic hypochromic anemia (16 per cent) for the most part responded to iron therapy In the patients with normocytic anemia associated with a reduction in the mean corpuscular hemoglobin concentration (26 per cent of the cases) iron therapy resulted in only partial alleviation of the anemia The patients with normocytic (30 per cent) or microcytic anemia (16 per cent) without reduction in the concentration of hemoglobin in the red cells failed to respond to iron therapy this type of anemia was primarily seen in those patients with a protracted course and moderate fever of long standing

Similar observations in tuberculosis have been reported by Braverman (12) The anemia accompanying brucellosis has been reported as being macrocytic and "hyperchromic" but these conclusions are not in accord with the data offered in support of this statement (21) The anemia was only slightly macrocytic (M C V 95 c μ) and the mean corpuscular hemoglobin concentration was in the normal range Harris (60) states that in brucellosis the hemoglobin and red cell count are usually reduced proportionately

In summary it may be concluded that in most instances of anemia associated with infection there is no significant alteration in the morphology of the red cells Macrocytosis of any important degree is extremely rare or never occurs In a few patients especially in those with an active disease process of long standing the anemia may become slightly microcytic and/or hypochromic Rarely however is the microcytosis or hypochromia as marked as in iron deficiency anemia

V BONE MARROW

It may be safely stated that bone marrow differential counts show no single change which is consistently present (85) It is generally true however that the myeloid–erythroid ratio is increased (28) Whether this is because of an increase in the myeloid elements or a decrease in the erythroid forms or is due to both an increase in the myeloid series and a decrease in the erythroid series is difficult to answer Bone mar

row biopsy except in some patients with overwhelming sepsis generally reveals a diffuse hyperplasia (122).

The most detailed studies of the morphology of the bone marrow cells during infections have been done by Hemmeler (64). He performed 32 sternal punctures in 25 patients with chronic infection and anemia. Of these 15 were done during the time when the reticulocytes in the peripheral blood were decreased. In 11 of the 15 the percentage of normoblasts was decreased below normal. During the stage of the infection in which the reticulocytes in the peripheral blood were decreased the basophilic type of normoblasts predominated and ortho-

TABLE IV

CHANGES IN PROPORTIONS OF VARIOUS TYPES OF NUCLEATED RED BLOOD CELLS IN BONE MARROW (64)

Type of Normoblast	Normal		Infection		During Recovery	
	Mean	Range	Mean	Range	Mean	Range
Basophilic	5	1–10	10	5–19	22	13– 36
Polychromatic	9	2–19	10	3–14	44	18–117
Orthochromatic	16	6–29	4	1– 9	32	13– 47
Total	*30*		*24*		99	

Figures represent numbers of cells per 100 of the nucleated cells in the marrow.

chromatic normoblasts and reticulocytes in the bone marrow were decreased. When the anemia had been present for a considerable time the basophilic normoblasts were somewhat larger than normal in size and the nuclei appeared quite immature. The polychromatic forms were also somewhat larger than normal. At the time when the reticulocytes in the peripheral blood increased the proportion of normoblasts increased markedly and orthochromatic normoblasts and bone marrow reticulocytes became numerous. These changes are summarized in Table IV. Hemmeler has interpreted these findings as revealing a maturation arrest of erythropoiesis. Somewhat similar conclusions have also been reached by Rohr (119), Saifi and Vaughan (122), Leitner (85) and Muller (102). Our own studies (28) have not confirmed those of Hemmeler but they have been neither as detailed nor as extensive as was his investigation.

STUDIES ON BLOOD DESTRUCTION

The usual evidences of hemolysis are lacking in most patients with chronic infection. Clinically jaundice is absent. The reticulocytes in the peripheral blood are decreased during the time when the anemia

is slowly developing Examination of the peripheral blood smear fails to reveal such evidences of exaggerated erythrocyte regeneration as polychromatophilia and nucleated red blood cells There is no increase in serum bilirubin or in urine or stool urobilinogen excretion (8,28 42 63 109 122 156 163 167) These statements do not however apply to all cases and especially not to patients with septicemia or overwhelming sepsis

The above evidence furthermore does not conclusively rule out the possibility that an increased rate of destruction of red cells is present Recently by the use of the selective red cell agglutination technic it was shown that in patients with leukemia and "lymphomas" the rate of destruction of erythrocytes is markedly increased although the usual evidences of hemolytic disease such as reticulocytosis hyperbilirubinemia or a positive Coombs test were absent (120)

Studies on the survival time of erythrocytes in patients with chronic infection have been reported in only a small group of patients Mollison (100) studied 6 patients with chronic sepsis In each case normal survival of the donor erythrocytes was observed Brown *et al* (15 16) obtained similar results in 4 patients whereas in a fifth patient with pneumococcal empyema the average erythrocytes survival time was 42 days Tischendorf *et al* (148) found a red cell survival time of approximately 90 days in a patient with empyema Following the intravenous injection of radioactive iron into 6 patients with infection Finch *et al* (44) obtained radioiron utilization curves with gradual daily increments characteristic of decreased red cell production Except in 2 patients with subacute bacterial endocarditis the rapid initial rise and early plateau in the utilization curves characteristic of hemolytic anemia were not observed In patients acutely ill with bacterial invasion of the blood stream all observers are in agreement that the survival time of the erythrocytes is markedly decreased (44 148)

Further studies on the survival time of erythrocytes in patients with chronic infection without bacterial invasion of the blood stream are needed before it can be definitely concluded that hemolysis plays no role in the pathogenesis of this type of anemia However most of the evidence which has been presented to date fails to support this possibility

IRON METABOLISM

In patients with this type of anemia there is a profound disturbance in iron metabolism as manifested by a decreased rate of iron utiliza

row biopsy except in some patients with overwhelming sepsis generally reveals a diffuse hyperplasia (122)

The most detailed studies of the morphology of the bone marrow cells during infections have been done by Hemmeler (64) He performed 32 sternal punctures in 25 patients with chronic infection and anemia Of these 15 were done during the time when the reticulocytes in the peripheral blood were decreased In 11 of the 15 the percentage of normoblasts was decreased below normal During the stage of the infection in which the reticulocytes in the peripheral blood were decreased the basophilic type of normoblasts predominated and ortho

TABLE IV

Changes in Proportions of Various Types of Nucleated Red Blood Cells in Bone Marrow (64)*

Type of Normoblast	Normal		Infection		During Recovery	
	Mean	Range	Mean	Range	Mean	Range
Basophilic	5	1–10	10	5–19	22	13– 36
Polychromatic	9	2–19	10	3–14	44	18–117
Orthochromatic	16	6–29	4	1– 9	32	13– 47
Total	30		24		98	

* Figures represent numbers of cells per 100 of the other nucleated cells in the marrow

chromatic normoblasts and reticulocytes in the bone marrow were decreased When the anemia had been present for a considerable time the basophilic normoblasts were somewhat larger than normal in size and the nuclei appeared quite immature The polychromatic forms were also somewhat larger than normal At the time when the reticulocytes in the peripheral blood increased the proportion of normoblasts increased markedly and orthochromatic normoblasts and bone marrow reticulocytes became numerous These changes are summarized in Table IV Hemmeler has interpreted these findings as revealing a maturation arrest of erythropoiesis Somewhat similar conclusions have also been reached by Rohr (119) Saifi and Vaughan (122) Leitner (85) and Muller (102) Our own studies (28) have not confirmed those of Hemmeler but they have been neither as detailed nor as extensive as was his investigation

STUDIES ON BLOOD DESTRUCTION

The usual evidences of hemolysis are lacking in most patients with chronic infection Clinically jaundice is absent The reticulocytes in the peripheral blood are decreased during the time when the anemia

utilization of the radioactive iron When erythropoiesis is normal this approaches 80 per cent

In patients with the anemia of infection the rate of incorporation of intravenously injected radioiron is markedly reduced (Fig 2) (44 48) This is particularly true during the first few days after the administration of iron Thereafter the uptake of iron by the red cells

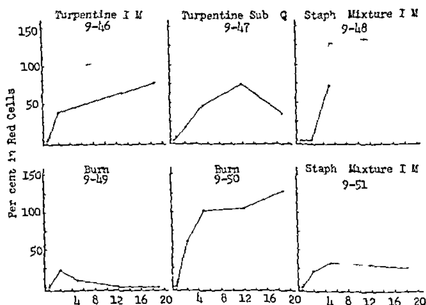


Fig 3 —Influence of acute inflammation on uptake of intravenously injected radioactive iron (Fe^{59}) by red cells of iron-deficient pigs (172) In all instances small amounts of iron were given (10 µg /kg body weight) Broken lines represent uptake before experimental procedure was carried out continuous lines indicate uptake after inflammation was produced Note that in every instance but one uptake was conspicuously retarded whether turpentine or a bacterial culture was injected or a burn produced

in a limited series of cases was found to be roughly proportional to the severity of the infection

From these studies it may be concluded that in the presence of infection the synthesis of hemoglobin is impaired It does not necessarily follow that the synthesis of hemoglobin is impaired because of an inability to utilize iron if hemoglobin synthesis were impaired from any cause the incorporation of iron into hemoglobin would be reduced Similar impairment in the uptake of intravenously injected ra

tion for hemoglobin synthesis a persistently low level of iron in the plasma *a decrease in the concentration of the iron transporting protein in the plasma* a minimal rise in plasma iron following the oral administration of iron and rapid removal of injected iron from the blood stream

UTILIZATION OF IRON FOR HEMOGLOBIN SYNTHESIS When single tracer doses of radioactive iron (Fe and Fe^{59}) are given intravenously

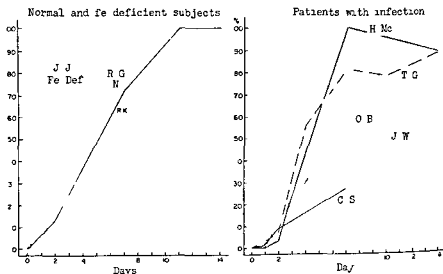


Fig 2 —Uptake of 3 to 5 mg intravenously injected radioactive iron (Fe^{59}) by the red cells of normal (N) and iron deficient (Fe Def) patients and in patients with various infections (48)

In patients with severe infections (C S and J W) not only was there delay in uptake but uptake was never complete in those less ill (O B T G and H Mc) less difference from uptake in normal individuals was observed

C S had chronic suppurative arthritis and chronic pyelonephritis volume of packed red cells (V P R C) was 28 ml /100 ml blood J W had subacute bacterial endocarditis V P R C 30 ml Both O B and T G had osteomyelitis V P R C 39 and 40 ml respectively H Mc had rheumatic fever V P R C 42 ml

to normal human subjects or to normal animals the radioiron rapidly enters the pool of iron used in hemoglobin synthesis and tagged erythrocytes begin to appear in the circulation within 24 hours Their number increases for 2 or 3 weeks Thereafter the radioactivity of the circulating red cells reaches a plateau This point indicates the extent of

100 ml the lowest 14 μg per 100 ml Of the 50 patients studied the plasma iron level was within two standard deviations of the normal mean in only one

Hypoferremia develops early in the course of an infection frequently

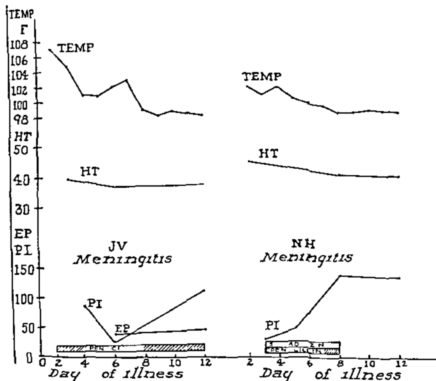


Fig 5—Effect of acute infection on plasma iron (P I) as exemplified in 2 patients (J V and N H) with meningococcal meningitis (26) Hypoferremia developed early in both iron values returned rapidly to normal as fever subsided no anemia developed and there was no increase in erythrocyte protoporphyrin (E P) Days of penicillin therapy indicated by hatching of sulfadiazine by open block

within 24 hours and is observed even in association with *acute* febrile diseases such as uncomplicated pneumonia meningococcal meningitis pharyngitis scarlet fever and otitis media (26 63) This is illustrated by the findings in 2 patients with acute meningococcal meningitis (Fig 5) When the illness is of short duration the plasma iron returns to normal as the fever subsides and no anemia develops In Figure 6 is shown

dioiron by the red blood cells has been observed in animals with experimentally induced infections (172) We have also found (172) that swine made deficient in iron animals which under such circumstances normally utilize iron very efficiently fail to incorporate injected iron into hemoglobin at the normal rate in the presence of experimentally induced infections sterile inflammation or burns (Fig 3) It

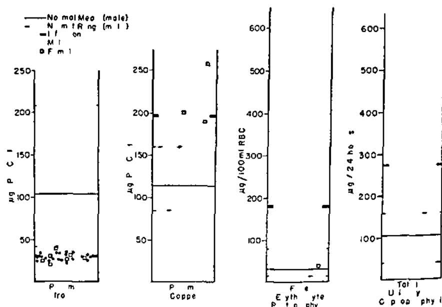


Fig 4—Plasma iron (50 patients) plasma copper (36 patients) free erythrocyte protoporphyrin (35 patients) and total urinary coproporphyrin (14 patients) in patients with anemia of infection

should be stated however that Yule *et al* (175) failed to confirm this observation in dogs

PLASMA IRON LEVEL Hypoferremia accompanying infections was observed as early as 1932 by Locke *et al* (89) Since that time many detailed accounts of the effect of infection on the plasma iron level have appeared (14 19 27 28 63 64 66 73 82 91 107 124 125 142 147 149 150 152)

In a study of 50 male patients with anemia associated with chronic infection we found a mean plasma iron level of 30 4±9 10 µg per 100 ml as compared with the mean plasma iron level of 105±30 3 µg per 100 ml in 50 normal male subjects (Table III Fig 4) The highest plasma iron level which was observed in these patients was 64 µg per

turns to normal Normal values are generally not attained until after the anemia has disappeared completely (Fig 7)

EXPERIMENTAL PRODUCTION OF HYPOFERREMIA In order to study in greater detail the changes in plasma iron which occur with infections and to learn something of the manner in which hypoferremia is brought

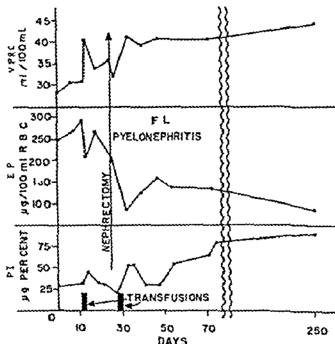


Fig 7 —Chronic infection (pyelonephritis patient F L) with anemia hypoferremia (P I) and increase in erythrocyte protoporphyrin (E P) (26) Kidney function was not diminished following nephrectomy anemia disappeared plasma iron rose and E P decreased

about a number of experimental studies have been carried out in animals (24 25 28 29 54 55 59 93 173) As illustrated in Figure 8 the intramuscular injection of a virulent culture of staphylococci into dogs is followed by marked hypoferremia (29) The plasma iron decreases rapidly during the first 24 hours of the infection and reaches a minimal value of about 30 μg per 100 ml in 24 to 48 hours There is then a progressive rise in iron to values well above the base line This hyperferremic "hypercompensatory" phase is of several days duration after which time the level returns to normal The hypoferremia precedes by

the effect of induced fever (typhoid vaccine) on the plasma iron in a human subject With each paroxysm of fever the iron decreased markedly but returned rapidly to normal after the cessation of fever No

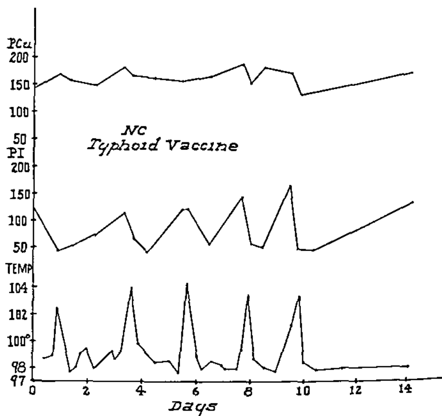


Fig 6—Effect of induced fever (typhoid vaccine) on plasma iron in a human subject (26) With each paroxysm plasma iron (P I) dropped markedly and returned to normal shortly after cessation of fever there was no significant change in plasma copper (P Cu)

anemia developed and there was no significant change in the plasma copper content

In patients with persistent infections the plasma iron remains low as long as the infection persists Since hypoferremia develops early in the course of an infection and occurs with mild infections hypoferremia is frequently present in the absence of anemia Only when the infection is severe enough and persists for a protracted time does anemia develop As the chronic infection subsides the plasma iron level slowly re

within 24 to 48 hours (Fig 9) This brief hypoferremic phase is followed by a gradual rise in plasma iron to normal levels and finally by a brief hyperferremic "hypercompensatory" phase on about the eighth postinjection day By the twelfth day following the injection of turpentine the plasma iron returns to normal It is again noteworthy that the hypoferremia is of brief duration and disappears before the height of

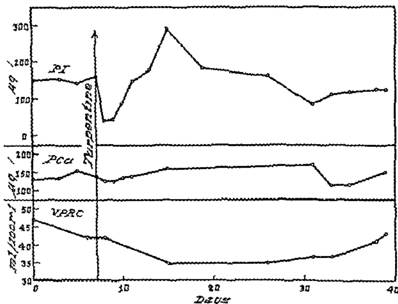


Fig 9 —Effects of intramuscular injection of 5 ml of turpentine on plasma iron (P I) plasma copper (P Cu) and volume of packed red cells (V P R C) of a dog (24)

the inflammatory reaction has been reached Thus although evidence of inflammation is present at the site of injection approximately 24 hours afterward the inflammatory reaction increases in extent and severity during the week following the injection During the second postinjection week swelling tenderness and edema persist and frequently the abscess spontaneously opens and drains Recovery then takes place rapidly during the third week The volume of packed red cells begins to decrease several days after the injection but maximal anemia does not develop until about the second week The anemia persists throughout the time of the inflammatory reaction and disappears as the inflammatory reaction subsides The hypoferremia therefore comes and goes

many days the development of anemia so that the maximal degree of anemia may be found during the time when the plasma iron is rising The sequence of events thus differs from that in patients in whom the

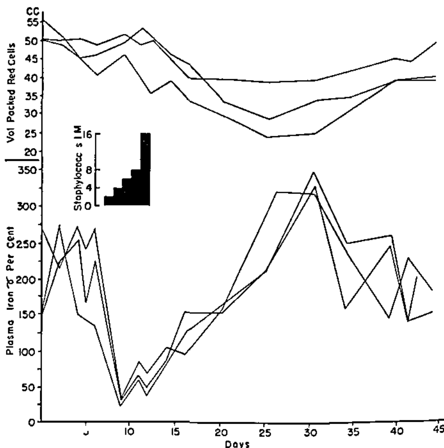


Fig 8 —Hypoferremia and anemia developing as result of production of staphylococcal abscesses in 3 dogs Abscesses healed after 3 to 4 weeks (29)

plasma iron level does not return to normal until some time after the anemia has completely disappeared

Neither bacteria nor their products are necessary for the production of hypoferremia in dogs the experimental production of a sterile abscess (turpentine) also being consistently followed by a marked fall in plasma iron (29) Like the effects of the injection of bacteria marked hypoferremia appears within 24 hours and reaches its lowest point

absorption of iron is unimpaired but the rate of removal of iron from the plasma is greatly accelerated (3) both the absorption of iron is impaired and iron removal from the plasma is accelerated

Evidence will be presented below that the rate of removal of iron from the plasma is greatly accelerated. Evidence will also be presented which shows that the absorption of iron may be impaired Thus the

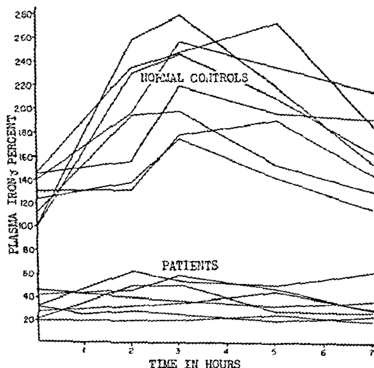


Fig 10 —Plasma iron level in 7 patients with chronic infections and in 8 normal individuals following ingestion of 1 Gm of ferrous sulfate (25)

third possibility mentioned above is probably the correct explanation for the failure to observe a rise in plasma iron after the administration of iron orally

RATE OF REMOVAL OF IRON FROM PLASMA Within 5 minutes after the intravenous administration of a single dose of iron ascorbate to normal human subjects the plasma iron increases 170 to 230 μg per 100 ml Thereafter there is a gradual decrease in the plasma iron content and the pre injection level is reached in 8 to 12 hours (Fig 11) Follow

before either maximal anemia or inflammation develops The explanation for this difference between dogs and man is not obvious

In order to determine whether or not hypoferremia could be induced by producing stresses other than that caused by the introduction of turpentine a variety of agents and procedures were employed in both rats and dogs (25 59) It was found that the injection of histamine epinephrine formaldehyde or horse serum produced a marked lowering of the plasma iron with maximal hypoferremia appearing approximately 8 hours after the injection Fracture of a bone was also followed by hypoferremia In this case however just as occurs following the injection of turpentine maximal hypoferremia appeared 24 hours later

In view of these findings the effects of the administration of adrenocorticotropic hormone (ACTH) and of adrenocortical extract were studied (25 59) It was found that the injection of either ACTH or cortical extract was followed by a decrease in the plasma iron which was maximal in 8 hours

In adrenalectomized animals the hypoferremia producing effect of ACTH is completely abolished and the hypoferremia which follows the injection of epinephrine is significantly less although not completely abolished whereas the hypoferremia producing effect of turpentine is unaltered (25 59 93)

Interpretation of these observations in animals in relation to the changes which occur in patients with infections is difficult They do however seem to indicate that "stress produced in various ways is associated with hypoferremia It is noteworthy that we have observed hypoferremia to develop also in human subjects under a variety of circumstances including traumatic shock and fracture It would seem that in the experimental animal and perhaps also in man the adrenal hormones play some role in the development of hypoferremia but that the adrenal cortex is not essential for this effect

EFFECT OF ORALLY ADMINISTERED IRON ON PLASMA IRON LEVEL Following the oral administration of 1 Gm of ferrous sulfate to normal human subjects there is an increase in the plasma iron level which reaches a maximum in 2 to 6 hours (Fig 10) In patients with hypoferremia associated with chronic infections little or no rise in plasma iron was observed after the administration of such a dose of iron (28) These results confirmed the findings of others (14 18 64 74 75 107 125)

There are three possible interpretations of this phenomenon (*1*) the absorption of iron is decreased in the presence of infection (2) the

2 Gm of elemental iron) in the form of the saccharated oxide (colloidal suspension) over a period of several hours to subjects with the hypoferremia of infection the plasma iron level is increased to 1 500 to 4 000 µg per 100 ml (79) However hypoferremia returns within 3 to 5 days following such injections This would seem to indicate that whatever the mechanism for rapidly removing iron from the plasma may be it is extremely powerful and cannot be overcome or satisfied easily

Several questions arise from this observation that iron even in excessively large amounts is removed rapidly from the plasma These will be discussed later

PLASMA IRON BINDING PROTEIN Studies by Cohn and associates (34 146) as well as those of Laurell (82 83) have demonstrated that iron is transported in the plasma bound to a specific protein (metal binding protein transferrin siderophilin) This protein has been identified as β_1 globulin and is found in Fraction IV 7 of Cohn's plasma fractions It has a molecular weight of approximately 90 000 and constitutes approximately 3 per cent of the total plasma proteins Two molecules of either Fe^{++} or Fe^{+++} are bound to one of protein Studies over a wide range of pH have revealed that at neutral pH the iron is non dialyzable whereas at pH 5 the iron becomes dialyzable

In normal human subjects 100 ml of serum or plasma are capable of binding approximately 359±30 8 (mean ±1 S D) µg of iron Normally about 35±6 4 per cent of the transferrin is bound to iron and the remainder is unbound but remains capable of accepting iron When inorganic noncolloidal iron is injected intravenously the iron is immediately bound by this globulin so that if sufficient iron is given the protein becomes completely saturated If more iron is given than can be attached to the protein the unbound iron rapidly leaves the blood stream and toxic symptoms such as flushing nausea vomiting and shock develop Thus the level to which the plasma iron rises following the parenteral injection of iron is limited by the iron binding capacity of the plasma only if this capacity is exceeded do toxic manifestations develop (31 82 116)

In patients with chronic infections not only is the plasma iron reduced but the iron binding capacity that is the quantity of transferrin is also reduced (31 82) In 13 patients with chronic infections studied in our laboratory the average iron binding capacity was found to be 195 µg per 100 ml (see Table III Fig 12) The reduction in plasma iron was however even greater than the reduction in the iron binding protein with the result that the per cent saturation of the protein with

ing the injection of a similar dose of iron in hypoferremic patients with chronic infections the plasma iron increases only 100 to 140 μg per 100 ml in 5 minutes and the pre injection hypoferremic levels are

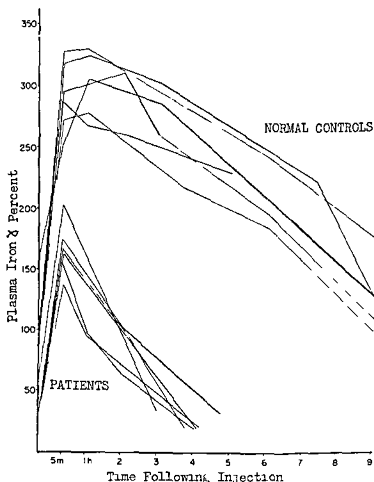


Fig 11 —Plasma iron level in 7 patients with chronic infections and in 6 normal individuals following intravenous administration of 0 5 mg of iron ascorbate per pound of body weight (28)

reached in 3 to 5 hours (28) Thus the rate of removal of iron from the plasma of patients with infections is about twice that seen in normal subjects This observation has been made by others as well (13 63 64 107 142 149)

By the intravenous administration of massive amounts of iron (1 to

of hypoferremia the severity of the anemia or the degree of reduction of the iron binding protein

The "braking" mechanism (inability to increase the plasma iron level beyond certain limits despite the intravenous administration of large doses of iron) described by Waldenstrom (159) as well as by

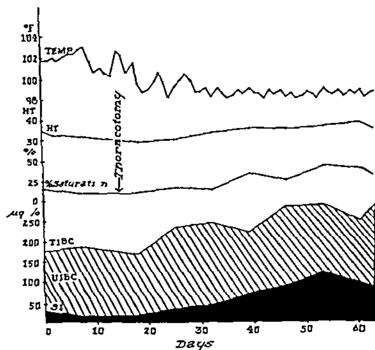


Fig 13 —Rise in iron binding capacity (T I B C) of serum rise in serum iron (S I) and minimal improvement in anemia in a patient (A R) following thoracotomy for a lung abscess (31) U I B C unsaturated iron binding capacity per cent saturation ratio of S I to T I B C

Greenberg *at al* (48) in this laboratory can be explained by these observations concerning the iron binding protein Normally there is a limit to the level to which the plasma iron can be raised by the intravenous injection of iron this limit being the quantity of transferrin present in the plasma In patients with infections the level to which the plasma iron can be artificially increased is limited still more by the reduced amount of iron binding protein which is present

The influence of the degree of saturation of the iron binding protein

iron was decreased from the normal of 35 per cent to an average of 16 per cent During recovery from infection there was a gradual rise in the quantity of transferrin to normal (Fig 13)

For several reasons it is unlikely that the hypoferremia results from reduction in the quantity of iron binding protein Restoration of circulating iron binding protein to the normal level by intravenous ad

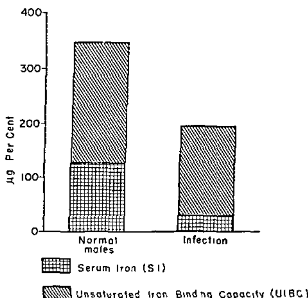


Fig 12 —Average total iron binding capacity of serum unsaturated iron binding capacity and serum iron in 13 patients with chronic infections compared with 15 normal subjects Average per cent saturation of protein with iron (S I/T I B C) in patients was 16 as compared with 36 per cent in the normal subjects

ministration of this protein does not cause the plasma iron level to return to normal and does not prevent the rapid disappearance of intravenously injected iron (Fig 14) The acute hypoferremia produced in human subjects by the injection of typhoid vaccine is not accompanied by a decrease in the iron binding capacity of the plasma In dogs given injections of turpentine or staphylococci intramuscularly the fall in plasma iron precedes the fall in the iron binding capacity In both dogs and patients with infections even though the quantity of iron binding protein is diminished a substantial amount of unbound protein remains because there is an even greater decrease in plasma iron than in transferrin Finally there appears to be no correlation between the degree

If the hypothesis put forward by Laurell is correct the question might be asked Does the reduction in the iron binding protein in patients with chronic infections indicate that the body has ample stores of iron and that the lowering of iron binding protein represents an attempt to reduce the absorption of iron? Contradicting this view is the fact that even though the concentration of protein is reduced there is a proportionately greater reduction in the plasma iron with the result that the saturation of the protein with iron is decreased below the normal

TISSUE IRON As discussed in the previous sections iron is removed rapidly from the plasma of patients with infection The question arises as to where this iron goes

In an attempt to answer this question the tissue distribution of intravenously injected radioiron was studied in rats and in dogs in which infection or sterile inflammation had been produced experimentally (49) The results of these studies indicated that the iron is removed mainly by the liver and to some extent by the spleen In rats given turpentine intramuscularly approximately 60 per cent of the amount of radioiron injected was found in the liver whereas in the control animals only about 37 per cent was localized in this organ Only 15 per cent of the injected dose appeared in the hemoglobin of the animals with inflammation whereas approximately 35 per cent of the radioiron injected was found in the hemoglobin of the control animals Thus the increase of iron in liver and spleen in the animals with inflammation was apparently at the expense of the iron which should have been used for hemoglobin formation The inflamed tissue itself accounted for only an insignificant proportion of the total dose of radioiron

These results are in agreement with those of Schaefer (126 128 129 130) but are somewhat at variance with those of Menkin (96 97) who claimed that large quantities of iron became fixed in the inflamed tissue In another attempt to determine whether an amount of iron sufficient to impair erythropoiesis is diverted to the area of inflammation a patient with a draining pulmonary fistula was given 0 3 Gm of saccharated oxide of iron intravenously and iron analyses were performed on the purulent material before and after the administration of iron (79) No increase in the iron content of the pus was observed

The results of these studies appear to indicate that the liver and spleen of animals with inflammation remove the iron from the plasma Apparently the same is true in patients with infections (79) 2 such

on the absorption of iron from the gastrointestinal tract is not known Laurell (82) has advanced the hypothesis that the degree of saturation regulates iron absorption This hypothesis is based on the fact that in conditions in which the demands of the body for iron are great such as iron deficiency and during pregnancy the plasma iron level is low and

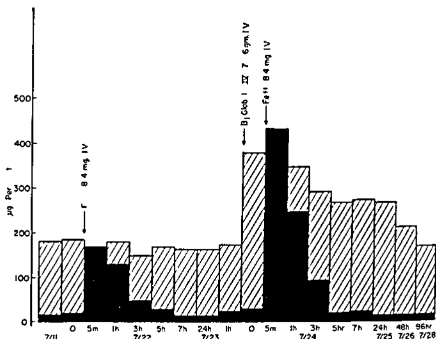


Fig 14 —Injection of β globulin (Fraction IV 7) increased total iron binding capacity of serum Injection of 8 4 mg of iron following administration of the globulin caused a greater rise in serum iron than before the globulin was given However the increase in iron binding capacity did not prevent the rapid disappearance of iron from the serum (31) Solid areas represent serum iron hatched areas unsaturated iron binding capacity total height of each column represents total iron binding capacity

the iron binding protein is increased above normal On the other hand in conditions characterized by excessive stores of iron such as pernicious anemia in relapse hemolytic anemia and hemochromatosis the iron binding capacity is decreased and the plasma iron level is elevated Rath and Finch (116) have challenged this hypothesis since they have observed that in animals fed diets which allow excessive iron absorption the iron binding protein is saturated with iron after about 2 weeks yet iron absorption continues rapidly over the next 3 to 4 weeks

the plasma iron of patients with infections to rise after the oral administration of iron as discussed earlier could be interpreted as a failure to absorb iron However evidence for another explanation has been offered the iron is removed so rapidly from the plasma that an increase in the plasma iron never occurs Nevertheless this does not preclude the possibility that the absorption of iron is decreased as well

Because of the relatively small portion of ingested iron which is absorbed under normal circumstances iron balance studies in human subjects are exceedingly difficult to carry out accurately (40) Studies were therefore made in rats by feeding radioactive iron and then after a given time determining the total amount of radioiron retained in the body by ashing the whole carcass (54) By this means it was possible to determine accurately the effect of infection on the absorption of iron The results of these studies indicated that the absorption of iron is decreased during the period of infection The control animals retained 22 per cent of the radioiron given over a 15 day period whereas the animals in which a staphylococcal abscess had been produced retained only 15 per cent Similar results were obtained in animals in which sterile (turpentine) abscesses had been produced (55) Likewise it can be shown (54) that the total body nonradioactive iron increases more slowly in growing rats with an experimentally induced infection than in control animals (Fig 16) This decrease in absorption of iron is reflected in a lowering of liver iron as compared with that of control rats At first glance this last observation would seem to be at variance with the previous statements that injected iron is rapidly taken up by the liver and that liver iron is increased in patients and animals with infections The explanation probably lies in the fact that over the short experimental period used in the rat experiment anemia did not develop and consequently the iron from hemoglobin breakdown was not being deposited in the liver in appreciable quantities

These results are at variance with those of Schaefer (125 126 128 129) He carried out iron balance studies in children with infections as well as tissue iron analyses of mice with experimentally induced infections and concluded that during the febrile period the absorption of iron from the gastrointestinal tract is increased It is difficult however to accept his data because of the many technical difficulties encountered in balance studies the small number of mice used in his experiments and the extremely small differences which he observed in the iron content of the tissues of the various groups

Studies of the iron content of the liver and spleen of patients dying

patients whom we treated with 1 6 and 2 2 Gm of saccharated oxide of iron died later and 46 to 88 per cent of the injected iron could be accounted for in the liver and spleen

To which cells in these organs the iron goes cannot be stated with certainty We have observed however that the intravenous administration of colloidal thorium dioxide to dogs results in a marked hyper

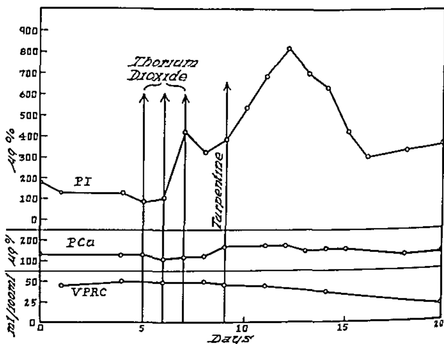


Fig 15 —Effects of three intravenous injections of colloidal thorium dioxide (2 ml /Kg body weight) on plasma iron (P I) plasma copper (P Cu) and volume of packed red cells (V P R C) of a dog Note failure of turpentine (5 ml intramuscularly) to produce hypoferremia when given after the thorium (24)

ferremia (24) (Fig 15) Furthermore in dogs so treated the hypoferremia which is associated with the injection of histamine or turpentine failed to develop This together with the histologic observation that iron accumulates in reticuloendothelial cells (45 63 152) suggests that it is the latter which receive the iron from the plasma Whether or not under these conditions the parenchymal cells of the liver and spleen also participate in this function is unknown but quite possible (45)

ABSORPTION OF IRON FROM GASTROINTESTINAL TRACT The failure of

whereas total starvation of 24 hours has little or no effect on the plasma iron level It should also be recalled that the intravenous administration of massive doses of iron has failed to relieve the hypoferremia or the anemia (79)

EXCRETION OF IRON It has been demonstrated quite convincingly that under normal circumstances iron is not excreted from the body

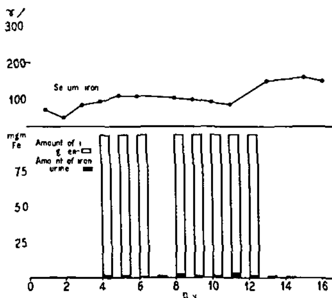


Fig 17 —Urinary excretion of iron in a patient (P L) with chronic pulmonary disease following multiple intravenous injections of iron (29) Total iron given intravenously 800 mg total urinary excretion of iron 12 mg percentage of iron excreted in urine 1 5

except in minute amounts Even when the body stores of iron are excessive the excretion of iron is not increased In this sense the metabolism of iron represents a "closed system"

Likewise there is no evidence to indicate that the excretion of iron is increased in patients with infections (88 125) Thus after the administration of large amounts of iron intravenously the urinary excretion of iron in patients represented only 1 5 to 7 0 per cent of the intravenous dose (Fig 17) (79) In dogs with experimentally induced inflammation less than 0 1 per cent of the intravenously administered isotopic iron was recovered in the excreta (urine plus stool) (49)

of various infections have in general revealed an increase in total splenic iron but no consistent change in liver iron has been observed (52 123) Such studies however do not indicate accurately the amount of iron absorbed since they do not take into account the increase in tissue iron which results from a shift in iron from hemoglobin to the

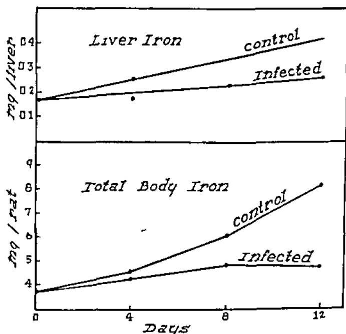


Fig 16—Effect of experimentally induced infection (staphylococcal abscesses) on absorption of iron by the rat Both control and infected groups were given the same amount of iron orally over the 12 day experimental period At the various time intervals total body iron and liver iron were determined Infected animals retained less iron than did the controls This decreased absorption of iron was reflected in lowering of liver iron No significant anemia developed in this period

tissues as the consequence of a decrease in total circulating hemoglobin

It is important to recognize however that even though anorexia commonly accompanies infections and the dietary intake as well as the absorption of iron are reduced, it is unlikely that decreased absorption of iron from the gastrointestinal tract plays a significant role either in the production of the hypoferremia or in the anemia Hypoferremia frequently occurs as early as 24 hours after the onset of the infection

the plasma copper level is observed within 24 hours and reaches maximum values of approximately 225 μg per 100 ml in 5 to 7 days This represents an increase of approximately 250 per cent As the inflammation subsides the plasma copper decreases (81)

The factors which regulate the plasma copper level are not known Holmberg and Laurell (67 68) isolated a blue protein coeruloplasmin from the serum of man This protein contains 90 per cent if not all of the copper in the serum Coeruloplasmin has been found to be an α globulin with a molecular weight of about 151 000 and contains 8 atoms of copper It can be reduced to a colorless compound with certain reducing agents a reduction which is completely reversible in the presence of oxygen

Studies on the copper content of human serums in relation to the α globulin component measured electrophoretically reveal a close correlation between the α 2+α 3 fraction and copper (23) In patients with infections and hypercupremia as the infection subsides the copper and the α 2+3 globulin content of the serum both decrease simultaneously Furthermore those clinical conditions which are associated with hypercupremia are in general also accompanied by an increase in α globulins in the serum This would suggest that one factor in the control of the plasma copper level is the copper-binding protein α globulin

The function of coeruloplasmin is not known Holmberg and Laurell (69) observed that when a purified preparation of this copper globulin was added to normal human plasma a marked increase in the histaminolytic activity of the plasma took place (84) On the basis of this they suggested that the blue globulin may be a component of the histaminolytic enzyme system Rottger and Stuttgen (121) have observed a correlation between the serum copper level and serum histaminase activity in pregnancy These observations are in need of confirmation

It seems unlikely that coeruloplasmin serves the purpose of transporting copper from the gastrointestinal tract since unlike the globulin which transports iron it is entirely bound to copper under normal circumstances and none is free to take up additional amounts of copper Furthermore after the oral or intravenous administration of a relatively large quantity of copper to a normal dog it can be demonstrated that this additional copper in the plasma reacts directly with diethyldithiocarbamate even though it is in the main nondialyzable (81) On the other hand the original coeruloplasmin does not show this reaction This would suggest that only a negligible quantity of the

COPPER METABOLISM

In patients with chronic infection there is a marked increase in the amount of copper in the plasma Little is known about the significance of this observation or concerning other aspects of copper metabolism such as absorption excretion storage or the function of the plasma copper

PLASMA COPPER In 1928 Krebs (78) discovered that the serum copper level of patients with infections is increased His results have since been verified by a number of investigators including Heilmeyer *et al* (62) Gorter (47) Cartwright *et al* (23 26 28) Munch Petersen (103) van Ravensteijn (154) and Robinson (117)

In a study of 36 patients with anemia associated with chronic infection we found a mean plasma copper level of 197±43 μg per 100 ml as compared with a mean value of 114±15 μg per 100 ml in 52 normal human subjects (*see* Table III) In all of the patients studied the plasma copper level was above the normal mean and in all but 8 patients it was increased beyond two standard deviations above the normal mean (*see* Fig 4) As the infection subsided the copper level returned to normal more rapidly than did the plasma iron and became normal by the time the anemia disappeared Hypercupremia has been observed frequently in patients with chronic infections in the absence of detectable anemia

Hypercupremia is also present in patients with relatively mild infections It occurs within several days after the onset of such infections as infectious mononucleosis (103) pharyngitis and even the common cold (62) As soon as the infection subsides the plasma copper returns to normal However we have not observed hypercupremia following induced fever in man (*see* Fig 6) This is somewhat at variance with the observations of Heilmeyer *et al* (62) who regularly found an increase in plasma copper level in animals following injections of milk bacterial toxins and vaccines

Hypercupremia is seen not only in infections it has been observed rather consistently in patients with acute leukemia chronic leukemia various forms of lymphoma disseminated lupus erythematosus and acute rheumatic fever (23) Normal pregnancy is also accompanied by a marked increase in plasma copper especially in the last trimester (43)

Hypercupremia can be produced experimentally in rats by the intramuscular injection of either staphylococci or turpentine An elevation in

PORPHYRIN METABOLISM

In patients with infections there are changes in porphyrin metabolism as manifested by an increase in the amount of free protoporphyrin in adult red cells and an increased excretion of coproporphyrin in the urine

FREE ERYTHROCYTE PROTOPORPHYRIN The amount of free protopor

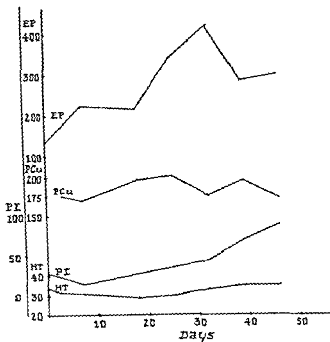


Fig 18 —Patient (A R) with chronic infection (lung abscess) with anemia (HT volume of packed red cells in ml /100 ml) hypoferremia (P I in µg per cent) hypercupremia (P Cu in µg per cent) and an increase in free erythrocyte protoporphyrin (E P in µg /100 ml of red blood cells) (26) Hypoferremia and hypercupremia developed early The maximal rise in E P occurred later when the anemia was most severe This patient was unusual in that plasma iron rose despite persistent anemia P I plasma iron P Cu plasma copper

phyrin isomer type III number 9 in the erythrocytes of patients with the anemia of chronic infection is greatly increased (26,28 51) In 35 patients studied the mean value for free erythrocyte protoporphyrin was found to be 180 µg per 100 ml of red cells as compared with a normal mean of 32 µg (*see* Table III) A significant increase (2 S D

copper normally present in plasma represents copper in transport and that copper while being transported is loosely bound to other proteins

Surgenor *et al* (146) have shown that the iron binding protein (β_1 globulin Fraction IV 7) is capable of uniting reversibly with copper Although this protein preferentially binds iron and the addition of copper to serum does not affect its iron binding capacity it is still possible that this protein functions at least under certain circumstances as a transport protein for copper Copper bound to this protein *in vitro* reacts directly with diethyldithiocarbamate (81)

WHOLE BLOOD AND RED CELL COPPER As shown in Table III there is an increase in whole blood copper as well as in plasma copper in patients with chronic infection This increase in whole blood copper is due mainly to an increase in plasma copper Our results (81) would *seem to indicate that in an occasional patient with chronic infection* the amount of copper in the red cells is slightly increased in the majority the red cell copper is within the normal limits In animals in which bacterial or sterile intramuscular abscesses had been produced we observed a modest increase in red cell copper These results are at variance with those of Heilmeyer *et al* (62) who found a reduction in the content of copper in the erythrocytes and postulated that in infectious diseases there is a shift in the copper from the cells to the plasma Munch Petersen (104) failed to find any significant change in cellular copper in human subjects in spite of considerable fluctuations in serum copper Thus it would seem that in patients with infection there is no shift of copper from the cells into the plasma

Why there is an increase in plasma copper in infections the source from which the copper is mobilized and what function or functions it serves as stated before are not known Since the increase in plasma copper develops in acute infections without the occurrence of any obvious alterations in erythropoiesis it is possible and even likely that this change is unrelated to erythropoiesis It might be although this is entirely speculative that the copper is related to the antigen antibody system and functions in some way in the defense mechanism of the body Other possibilities are that the altered copper metabolism is a manifestation of the increased metabolic activity of the cells or that the copper is simply a product of the destruction of cells The plasma copper level is generally elevated in conditions associated with an increase in the plasma content of fibrinogen α globulin mucoprotein polysaccharide or hexosamine

164 165) However urine from patients with acute poliomyelitis regularly contains predominantly the type III isomer (166)

Whether the increased amount of coproporphyrin I in the urine of patients with infections represents actual overproduction of the porphyrin or merely a diversion in its excretion from the bile to the urine as the result of impaired liver functions is difficult to state without careful analyses on both urine and stool simultaneously However there are but two conditions under which an overproduction of the type I isomer may be anticipated porphyria a constitutional metabolic fault and in the presence of increased erythropoietic activity (164) Since there is evidence of decreased rather than increased erythropoietic activity in patients with infections and since it is well established that slight impairment of liver function is present in febrile patients the most likely explanation of the increased excretion of coproporphyrin I is that there is simply diversion from the bile to the urine rather than overproduction This concept is in agreement with that of Watson (164)

The cause of the increased excretion of the type III isomer in patients with acute poliomyelitis is obscure Watson (166) has considered the possibility that under these circumstances the type III isomer may be derived from the central nervous system

PROTEIN METABOLISM

Nitrogen Metabolism During the acute febrile stage of most infectious diseases there is a marked increase in the amount of nitrogen excreted in the urine (53 111–114) This results in the establishment of a negative nitrogen balance and consequently loss of body weight and has been referred to as toxic destruction of protein"

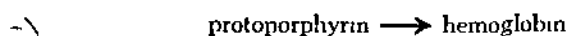
The duration of this protein catabolic phase varies and may persist after the symptoms and signs of the disease have disappeared It is a self limiting process however not being encountered in patients with chronic infectious diseases Evidently as the nutritional status of the patient deteriorates the excessive loss of nitrogen gradually diminishes and finally the nitrogen balance becomes positive and remains positive even in the face of renewed insults Thus only previously healthy well nourished individuals respond to infections by wasting protein

This phenomenon appears to be an integral part of the reaction to injury and is accompanied by a reduction in serum albumin lipids and amino acid nitrogen As yet no satisfactory explanation has been found

above the normal) was observed in 27 (77 per cent) of the patients (*see* Fig 4) Values greater than 200 μg per 100 ml were observed in 12 of the patients

In acute infections with hypoferremia but without anemia no increase in free erythrocyte protoporphyrin has been observed (*see* Fig 5) Only when the infection persists for a month or more or when significant anemia develops does the rise in protoporphyrin occur (Fig 18) Frequently the increase reaches its maximum only after the maximal degree of anemia has been attained Return of the erythrocyte protoporphyrin level to normal takes place slowly and often normal values are not reached until long after the anemia has disappeared (*see* Fig 7) The degree of rise in erythrocyte protoporphyrin seems to be correlated with the duration of the infection and to a lesser extent with the severity of the anemia

The increase in protoporphyrin in the circulating erythrocytes in the absence of a reticulocytosis is interpreted as indicating that the synthesis of hemoglobin up to the stage of formation of protoporphyrin 9 proceeds satisfactorily but that there is a slowing of the reaction



This interpretation is suggested by the observation that in patients with iron deficiency where the reaction



is known to be retarded the protoporphyrin content of the erythrocytes is markedly increased

COPROPORPHYRIN EXCRETION The urinary excretion of coproporphyrin in patients with infections is increased (28) By the use of a colorimetric method for the determination of coproporphyrin we have observed values as high as 550 μg per 24 hours whereas normal subjects excrete 40 to 150 μg per 24 hours (*see* Table III Fig 4) The average daily excretion for 14 patients with infections was found to be approximately 275 μg

These results confirm those of earlier workers (38 156 165) In our studies (28) the isomer type was not determined This is regrettable since the interpretation of the coproporphyrinuria depends almost entirely upon knowing the isomer which is excreted in excess

Evidence has been presented by others that in the urine of patients with pneumonia lung abscess acute rheumatic fever infectious mononucleosis and infectious hepatitis the type I isomer predominates (38

164 165) However urine from patients with acute poliomyelitis regularly contains predominantly the type III isomer (166)

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PROTEIN METABOLISM

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This phenomenon appears to be an integral part of the reaction to injury and is accompanied by a reduction in serum albumin lipids and amino acid nitrogen As yet no satisfactory explanation has been found

for these phenomena The disturbance is characterized by impairment of synthesis of protein including serum albumin and a tendency to route products of protein metabolism preferentially to urea and ammonia Whether this is advantageous or disadvantageous to the body cannot be stated In any event it is an inevitable consequence of severe infection or injury and attempts to prevent it during the initial catabolic phase have been universally unsuccessful On the other hand in patients with chronic infections the ability of the body to synthesize protein appears to be intact and such synthesis does take place provided adequate amounts of protein are supplied in the diet (17)

Whether or not protein depletion as a result of this toxic destruction of protein is a significant factor in the pathogenesis of the anemia of infection is not known Waife *et al* (158) have presented evidence that after the protein reserves are replenished the hemoglobin level increases However their data are difficult to interpret since the infections were probably subsiding at the time when the protein reserves were being restored and a control series was not studied In our own experience (28) it has not been possible to alleviate the anemia by protein supplementation if the severity of the infection remained constant Metcoff *et al* (98 99) failed to observe a greater reduction in total circulating hemoglobin in protein depleted rats with experimentally induced infection than in uninfected protein depleted rats Furthermore adequate protein intake failed to prevent the anemia associated with infection in the rat Also contradicting the hypothesis that the anemia of infection is related to inadequate supplies of protein is the observation that swine made anemic by being fed a diet low in protein do not develop hypoferremia hypercupremia or an increase in free erythrocyte protoporphyrin (30) By these criteria at least the anemia of protein deficiency induced by inadequate intake of protein is quite different from the anemia of infection However none of these experiments completely eliminates the possibility that a disordered metabolism of protein is the cause of the anemia since the consequences of dietary restriction of protein may be quite different from those of an intrinsic metabolic defect in protein metabolism

Plasma Proteins Although the total plasma protein level may not be significantly altered from the normal in patients with infections numerous and rather striking changes in the various protein components take place (56 86) In the febrile stage of an acute infection there is usually an increase in fibrinogen and a marked increase in α globulin to several times its normal concentration In addition there is fre

quently a decrease in albumin which makes the rise in α globulin even more striking With the increase in the α globulin fraction the "C reactive protein" makes its appearance (1 95) and there is an accompanying increase in polysaccharide *hexosamine and mucoprotein content* (133 136 137 139) A later change in plasma globulins which accompanies virtually all types of infection is an increased concentration of the γ globulins (86) In many chronic infections there is a tendency for all three types of globulins to increase

It would seem that severe bodily injury of almost any sort (infections rheumatic fever rheumatoid arthritis carcinomatosis leukemia burns fractures and trauma) is accompanied by an increase in plasma fibrinogen α globulin hexosamine polysaccharide and mucoprotein fractions It is noteworthy that it is in many of these conditions that a mild anemia with hypoferremia hypercupremia and an increase in free erythrocyte protoporphyrin also occurs These changes in protein metabolism have been variously interpreted as indicating tissue destruction or tissue proliferation The relation of these many and diverse alterations in plasma proteins to the anemia of infection is obscure No doubt as knowledge is gained concerning the significance of these variations in the plasma protein constituents it will be easier to understand the changes which occur in iron copper porphyrin and bone marrow metabolism

COMPARISON WITH IRON DEFICIENCY ANEMIA

The anemia of infection resembles iron deficiency anemia in several respects (28) In both conditions the plasma iron level is low the plasma copper level *is increased and there is an increase* in the amount of free protoporphyrin in the erythrocytes (28) Likewise in both conditions iron is removed rapidly from the plasma with the result that after the oral administration of iron little or no rise in plasma iron is observed (28)

The anemia associated with infection differs from the anemia associated with iron deficiency in two important respects First the total iron binding capacity of the serum is decreased in the presence of infection while it is increased in patients with iron deficiency anemia (31) Values of 195 μg per 100 ml are found in the former condition whereas 450 to 600 μg per 100 ml is common in the latter It is of interest that when both conditions are present in the same individual the total iron binding capacity is either normal or somewhat decreased The other important difference between the anemia associated with infection and anemia

of iron deficiency is that the former is refractory to iron therapy (79)

As discussed previously the anemia of infection is usually normocytic and normochromic Under unusual circumstances especially with *infection of several years duration the anemia may become slightly* microcytic and slightly hypochromic Rarely however is the mycrocytosis and hypochromia as marked as in iron deficiency anemia Only once have we observed a mean corpuscular volume of less than 75 c μ in a patient with a chronic infection (28) In patients with moderately severe iron deficiency the mean corpuscular volume is usually less than 75 c μ and the mean corpuscular hemoglobin concentration is below 30 per cent It may be added that the anemia associated with chronic infection is usually mild in degree whereas iron deficiency anemia may become quite severe

COMPARISON WITH OTHER SIMPLE CHRONIC ANEMIAS

The term simple chronic anemia is used to refer to the normocytic or slightly microcytic anemia which accompanies many chronic systemic diseases in the absence of evidence of blood loss iron deficiency or bone marrow invasion (170) Morphologically these anemias cannot be distinguished from the anemia associated with infection In their insidious mode of onset chronic nature and unresponsiveness to the usual antianemic agents they also resemble the anemia of infection In other respects as well several of these anemias particularly that associated with rheumatoid arthritis malignancy trauma and rheumatic fever resemble the anemia of infection There is even some similarity between the physiological anemia of pregnancy and the anemia of infection Whether their pathogenesis is also similar to or identical with that of the anemia associated with infection cannot be stated with certainty because of the limited amount of data available

The anemia of nephritis and that associated with burns on the other hand differ from the anemia of infection in several respects as will be pointed out shortly The normocytic anemia associated with such conditions as chronic dysentery chronic ulcerative colitis parasitic infections leprosy and various endocrine disorders has not been sufficiently well studied for proper classification

RHEUMATOID ARTHRITIS Studies on plasma iron plasma copper and free *erythrocyte protoporphyrin in* 15 *patients* with active uncomplicated rheumatoid arthritis are summarized in Table V Hypoferremia was present in all 15 patients The plasma copper level was elevated in

11 and there was a significant increase in free erythrocyte protoporphyrin in 10 of the patients In addition lowered values for the total iron binding capacity of the serum were observed in the 7 patients in whom this determination was performed

As in patients with chronic infection following the oral administration of iron there is little or no rise in iron in the plasma and after the

TABLE X

CHEMICAL CHARACTERISTICS OF ANEMIA ASSOCIATED WITH VARIOUS OTHER SIMPLE CHRONIC ANEMIAS

Condition	No of Patients	Volume of Packed Red Cells Ml /100 Ml	Plasma Iron µg 100 Ml	Plasma Copper µg /100 Ml	Free Erythrocyte Protoporphyrin µg /100 Ml
Rheumatoid arthritis	15	3[illegible] (34 40)	35 (13 55)	165 (125 204)	127 (37 213)
Carcinoma	5	32 (23 39)	33 (14 59)	170 (110 219)	148 (44 235)
Hodgkin s disease	17	33 (20-39)	40 (15-94)	190 (150 222)	122 (47-322)
Fractures	5	39 (34-44)	41 (29 61)	173 (118 242)	61 (17 158)
Rheumatic fever	[illegible]	39 (35-44)	54 (38 71)	170 (114 225)	
Lupus erythematosus	6	30 (25 36)	72 (40 96)	122 (78 142)	
Renal disease	10	28 (18 38)	62 (15 115)	183 (136-240)	103 (18 198)
Pregnancy	22	38 (35-41)	59 (29 162)	261 (195 346)	53 (12 69)

[illegible]
Without ... complications ... infection
blood
[illegible]

intravenous injection of iron the rate of removal from the plasma is accelerated Iron therapy even massive intravenous therapy is without effect on the anemia (79) Only as the activity of the rheumatoid process subsides does the anemia disappear

Nilsson (107) in his comprehensive study of anemia in rheumatoid arthritis made observations similar to those noted above In addition he noted an increase in pronormoblasts and basophilic normoblasts in the marrow as compared with the normal These observations are similar to those of Hemmeler (64) in patients with chronic infection Thus in all essential respects the anemia associated with rheumatoid arthritis resembles the anemia of chronic infection

MALIGNANCY Five patients with various forms of advanced carcinoma without evidences of secondary infection blood loss bone marrow invasion by the carcinomatous process or "secondary" hemolytic anemia have been studied (Table V) Hypoferremia was observed in all 5 patients In 4 of them hypercupremia and an increase in free erythrocyte protoporphyrin were present Similar observations in regard to iron and copper were made by Heilmeyer *et al* (63)

We have studied 17 patients with well advanced Hodgkin s disease selecting patients without demonstrable infiltrative bone lesions complicating infections blood loss or hemolytic anemia (Table V) Hypoferremia was present in 14 In the remaining 3 the plasma iron level was in the lower range of normal In 15 patients hypercupremia was present while in 2 the plasma copper level was within the normal range A significant increase in free erythrocyte protoporphyrin was observed in 11 of the 17 patients

Since the anemias associated with either chronic sepsis or cancer are mild in degree morphologically comparable similarly unresponsive to iron or liver and associated with hypoferremia hypercupremia and an increase in free erythrocyte protoporphyrin it seems possible that their pathogenesis might also be similar This would not be too surprising necrosis of neoplastic tissue is not uncommon and it has been shown that many of the metabolic changes which occur with infections also take place in the presence of sterile inflammation Recently Shen and Homburger (135) have presented evidence that the anemia associated with malignancy like the anemia of infection responds in part at least to the administration of cobalt Ross *et al* (120) as well as Berlin (11) on the basis of differential cell survival studies have concluded that the anemia of leukemia and malignant lymphoma is due in large part to an increased rate of cell destruction Chemical studies such as those which have been used in the investigation of the anemia of infection have not been made in a large group of patients with cancer or leukemia Those studies which have been done (11 26) on the serum iron level in leukemia indicate that hypoferremia is not a consistent finding in this disease

TRAUMA During the first week or two following such injuries as fractures contusions or deep and extensive lacerations there is not uncommonly a moderate decrease in hemoglobin and red cells (157) A similar anemia may develop after operative intervention which has not been preceded by injury and has not been complicated by infection (132) Vaughan *et al* (157) presented evidence that the anemia fol

lowing trauma is not due to blood loss infection or hemolysis but rather to a disturbance in hemoglobin synthesis perhaps consequent to disordered protein metabolism or liver function

The results of a study of 5 patients with bone fractures are presented in Table V Hypoferremia was observed in all 5 and an elevation in the plasma copper level was noted in 4 of the patients A significant elevation in the free protoporphyrin concentration was present in only 2 patients The normal free erythrocyte protoporphyrin concentration noted in 3 of the patients might be explained by the fact that sufficient time had not elapsed for an increase to occur it has been noted that in patients with chronic sepsis this change develops later than the alterations in iron or copper

Many of the metabolic alterations which occur in patients with infections are also observed following trauma Whether the pathogenesis of the anemia is the same in the two conditions cannot be stated from these limited data The possibility does however deserve further study

COLLAGEN DISORDERS A mild anemia commonly accompanies such diseases as rheumatic fever disseminated lupus erythematosus periarteritis nodosa, and scleroderma Table V includes data on 7 patients with active rheumatic fever Hypoferremia was present in 6 the seventh patient had a low normal plasma iron level Hypercupremia was observed in 5 of the 7 patients Only 2 of 6 patients with disseminated lupus erythematosus whom we have studied were found to have hypoferremia and in none was the plasma copper level elevated Several European workers (62 63 150) have observed hypoferremia and hypercupremia in acute rheumatic fever Further work will have to be done in this group of diseases before any conclusions can be drawn

RENAL DISEASE The results of a study on 10 patients with various forms of renal disease are shown in Table V Except in the patients with active pyelonephritis no consistent change in plasma iron or copper or in free erythrocyte protoporphyrin has been observed The plasma iron was found to be normal in 6 of the patients and low in 4 An elevation in plasma copper and red cell protoporphyrin was present in 8 patients in 2 the values for both of these determinations were normal Loge *et al* (90) have likewise been unable to demonstrate a consistent pattern for either plasma iron or erythrocyte protoporphyrin in renal disease These workers observed that when chronic renal insufficiency was associated with a stable or slowly progressive anemia of moderate severity the utilization of intravenously administered radioactive iron was decreased the reticulocytes were not increased and there was no evidence

of increased hemolysis On the other hand in patients with chronic glomerulonephritis and marked azotemia with rapidly developing anemia evidences of increased hemolysis could be detected A similar observation has been made by Emerson (41)

From the above evidence it is apparent that the severe anemia associated with chronic renal disease is due not only to depression of erythropoiesis but is at times hemolytic in nature as well It may be that the pathogenesis of the anemia is somewhat different in the various types of kidney disease We have observed 3 patients with active pyelonephritis and mild anemia in whom the characteristic chemical pattern of the anemia of infection was found Until detailed studies on many patients in various stages of renal disease have been made an understanding of the pathogenesis of anemia in renal disease is not likely to be obtained

THERMAL INJURY Anemia following extensive thermal injury appears as soon as a few days after the injury and is frequently marked in severity and progressive in its course In the protracted convalescent period following even small burns moderate anemia is usually present Adequate evidence has been reported from several different laboratories (58 71 72 101 134) that the anemia which develops so early following burns is hemolytic in character However during the convalescent phase the mild or moderate anemia which is present is not accompanied by evidences of increased red cell destruction and is frequently associated with bacterial contamination of the burned area Moore *et al* (101) as well as James *et al* (71 72) have presented evidence that the anemia at this stage is due to a decrease in hemoglobin synthesis It is likely although it remains to be proved that this later anemia is either the same as or similar to the anemia of infection in its metabolic characteristics and pathogenesis The anemia might be the result of secondary infection in the burned area or the consequence of a sterile inflammation with tissue destruction

PREGNANCY Oddly enough there are certain similarities between the physiologic anemia of pregnancy and the anemia of infection (43 56 86 138) Morphologically these two types of anemia are indistinguishable In both there is a reduction in plasma iron an increase in plasma copper an increase in α globulin and an increase in serum polysaccharides (*see* Table V) However there are also as many dissimilarities Hypoferremia even in the last trimester of pregnancy is not as marked as in the anemia of sepsis (43) There is no significant increase in free erythrocyte protoporphyrin during pregnancy and the

total iron binding capacity of the serum is increased rather than de creased so that these two types of anemia are readily distinguishable

THERAPY

As pointed out previously anemia when present in association with infection is usually mild in degree and is rarely progressive in severity Whether or not the presence of such anemia is in any way detrimental to the patient is a problem which in the opinion of the writers never has been settled satisfactorily It is widely held as the result of uncon trolled clinical observations and impressions that in the presence of anemia the resistance of the host to the invading organism is lowered his well being is impaired convalescence is prolonged and his suscep tibility to shock resulting from minor trauma or surgery is increased Many regard blood transfusion to be a valuable therapeutic procedure in meeting these ill effects There are few experimental data however which either support or deny these views

Alleviation of the underlying infection is invariably followed by gradual relief of the anemia Obviously whenever this is possible it is the treatment of choice

WHOLE BLOOD TRANSFUSION Whole blood transfusions are effective in restoring the red cell mass to normal Whether or not such therapy is of any benefit to the patient is difficult to determine Certainly the in discriminate use of whole blood in all patients with this mild type of anemia is to be condemned

IRON The reduced dietary intake of iron during the febrile periods the reduced absorption of iron from the gastrointestinal tract the low rise in plasma iron after the oral administration of iron the rapid re moval of iron from the plasma the hypoferremia and the marked avidity of the tissues for iron are all features which suggest that iron deficiency may be an etiologic factor in the production of the anemia Nevertheless it is generally agreed that the oral administration of iron is without effect However it has been both claimed (63 141 152) and denied (28 48 107 124-126 143 149) that the anemia is alleviated by the parenteral administration of iron Vannotti and Delachaux (152) report that they obtained good results from parenteral iron therapy in chronic infectious diseases and state "At the same time as Heilmeyer we ourselves noted a distinct improvement not only of the general condition but also of the basic disease in a number of chronic febrile infections such as rheumatism pulmonary abscess osteomyelitis and

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above all pulmonary tuberculosis More acute inflammatory processes such as pneumonia and severe furunculas or whitlows will sometimes also react exceptionally well to intravenous injections of iron No data in support of these statements have been presented

The recent devolpment of a comparatively nontoxic intravenous iron preparation saccharated oxide of iron has made it possible to administer considerably larger amounts of iron intravenously than had

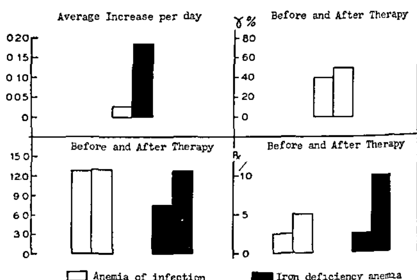


Fig 19 —Comparison of effects of intravenous iron therapy in anemia of infection and iron deficiency anemia (29) Hemoglobin did not increase 30 days after therapy in patients with infections whereas patients with iron deficiency anemia showed marked increase Reticulocyte response in the two groups also differed No significant change in serum iron took place in patients with infection

heretofore been practical In our own laboratory (79) by the use of this preparation the effects of massive amounts (1 0 to 2 2 Gm elemental iron) of intravenously administered iron have been observed in 14 patients with various chronic infections and anemia (Fig 19) Despite the large doses of iron given and the marked increase in plasma iron to levels of 3 000 to 4 000 μg per 100 ml immediately following treatment in no instance was the anemia relieved or the hypoferremia permanently corrected as long as the infection persisted From this it must be concluded that the anemia fails to respond to iron regardless of whether this agent is given orally or parenterally It is not surprising that opinions have differed as to the effect of such therapy if one con

siders the tendency of such anemias to subside spontaneously as the underlying disease improves

COBALT It was shown in this laboratory (173) that the administration of cobalt overcomes the retardation of hemoglobin formation *which is produced by experimentally induced inflammation in the rat* Furthermore not only does the administration of cobalt abolish the anemia producing effects of turpentine and produce polycythemia but it also increases the absorption of iron from the gastrointestinal tract to within the normal range (55)

Likewise it has been demonstrated that the oral administration of 20 to 60 mg of cobaltous chloride per day to patients with chronic suppurative infections as in the experimental animals results in alleviation of the anemia (10 118 168) Reticulocytosis is observed in about 6 days and this is followed by an increase in the volume of packed red cells blood volume and total circulating hemoglobin

The mode of action of cobalt is not clearly understood However there is evidence that cobalt inhibits the respiration of microorganisms as well as of animal tissues and tumors and that it does so by inhibiting a number of enzyme systems (20 87 108) Not only are several sulfhydryl dependent enzymes inhibited but cytochrome oxidase and catalase as well Oral therapy with sulfur containing amino acids such as cysteine and also to a lesser extent the administration of histidine inhibits the effect of cobalt in producing polycythemia in rats and parenterally administered cobalt–cysteine complexes do not produce polycythemia (108) Ascorbic acid also inhibits the effects of cobalt in producing polycythemia in rabbits and dogs (6 36) In view of these observations cobalt would appear to stimulate the bone marrow by causing generalized tissue anoxia

With regard to the advisability of treating patients with chronic infections it should be pointed out that rats with experimentally induced inflammation which are given cobalt grow at a slower rate than do animals with inflammation not given cobalt (173) Furthermore although cobalt to some extent alleviates the anemia of patients with chronic infections no concomitant improvement in the well being of the patients has been observed and the side effects of cobalt on the gastrointestinal tract particularly anorexia nausea and vomiting have been prominent (10 118) The value of such therapy must therefore be seriously questioned

HORMONES The administration of adrenocorticotropic hormone or cortisone to patients with active rheumatoid arthritis or active rheu

matic fever is followed by disappearance of anemia At the same time the active disease processes are inhibited or at least the inflammatory reaction associated with these diseases is suppressed so that it is difficult to ascribe to these hormones a specific direct effect on the erythropoietic tissue *It seems more likely that the anemia disappears as a* result of suppression of the inflammatory reaction Similar observations have not been made in patients with "anemia of infection" in the restricted sense employed in this paper

OTHER SUBSTANCES Purified liver extract copper ascorbic acid and iron ascorbate are without effect on the anemia of infection (28) Evaluation of the effectiveness of either oral or parenteral protein or amino acid therapy is difficult Adequately controlled studies in a large group of patients have not been made Such studies should be done and with these the effects of testosterone should be included In 1 patient we found the intravenous administration of globin cysteine and methionine to be without effect (28) As discussed previously adequate protein intake in the rat fails to prevent the development of anemia associated with infection (98 99) However since amino acids are essential for the fabrication of globin and since chronically ill patients are depleted of their protein reserves it is certainly logical to assume that optimal dietary intake of protein would be essential for the most rapid and complete alleviation of the anemia

DISCUSSION

From the data presented it is evident that in patients with infections there is a marked disturbance in iron metabolism These changes are outlined schematically in Figure 20 Since most patients with infections develop anorexia the dietary intake of iron is reduced somewhat below the normal The absorption of iron from the gastrointestinal tract at least in animals with experimentally produced infections is reduced Reduced absorption of iron is probably only a minor factor however Iron entering the plasma from all routes is taken rapidly to the liver and spleen with the result that a persistent hypoferremia develops The concentration of transferrin the iron transporting protein of the plasma is decreased Since anemia ensues iron must be diverted from the hemoglobin compartment into the plasma and immediately therefrom to the liver and spleen As a consequence there is an increase in the amount of iron in the depot organs

The mechanism which keeps the plasma iron level low *is not under*

stood The diminished absorption of iron from the gastrointestinal tract and the decreased concentration of transferrin in the plasma do not adequately explain the persistent hypoferremia Evidence has been presented that the adrenal cortex may play a role in this regard but that other factors are apparently of greater importance Evidently there is some alteration in the tissues themselves particularly the liver spleen

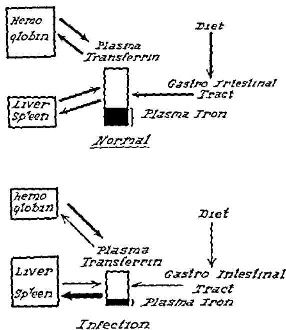


Fig 20 — Diagrammatic representation of iron metabolism in normal subjects and patients with infections Light arrow metabolic pathway is decreased heavy arrow metabolic pathway is overactive

and reticuloendothelial system which increases their avidity for iron Of special interest in this regard is the recent observation of Cohn and his group (33) that there is a specific protein in normal liver which is capable of rapidly removing iron from transferrin It is tempting to postulate that in patients with infection either the activity or the actual amount of this liver protein is greatly increased and that this is the explanation for the hypoferremia As yet however there are no experimental data to substantiate or to refute this interesting possibility

Several European investigators including Wallbach (160 162)

Hettche (65) Heubner and Heilmeyer (63) have presented evidence that the iron content of reticuloendothelial cells increases markedly during infection (152) These workers have offered the hypothesis that during infection the functional activity of the reticuloendothelial system is greatly increased and that increased amounts of iron are essential for these cells to carry on this activity The studies (4 5 24 25 130 147 153) on the effect of altering the activity of this system by the injection of various reticuloendothelial depressing and stimulating substances would seem to offer some but not conclusive support for this hypothesis On the basis of these observations and speculations as well as those of Gordon and Katsh (46) which indicated that the phagocytic activity of the reticuloendothelial system is under the control of the adrenal cortex one can theorize further that the secretory activity of the adrenal cortex is increased in patients with infections As a consequence of this certain functional activities of the reticuloendothelial cells are increased since iron is essential for these activities it is avidly taken up from the plasma by these cells with the result that hypoferremia is produced

There are many objections to this theory The observations which support it have been made in animals and may not apply to man In our laboratory we have been unable to produce hypoferremia in human subjects by the administration of either adrenocorticotropic hormone or cortisone (76) More recent studies in rats have failed to establish a clear cut relationship between adrenocortical activity and the plasma iron level (76) Although the work of Gordon and Katsh (46) indicates that cortical hormones stimulate the phagocytic activity of macrophages it does not necessarily follow that all functions of these cells are increased by this means Good evidence that in patients with chronic infection there is persistent adrenocortical hyperactivity is lacking Finally Finch *et al* (45) have presented evidence that under certain circumstances the parenchymal cells of the liver kidneys and other organs may participate in the storage of iron Unfortunately these workers did not study animals or patients with infection to assess the role of the parenchymal cells in regard to iron uptake during infection Nevertheless it is possible that these cells are as important in this regard as are the cells of the reticuloendothelial system

Whether in patients with infection iron is simply stored in the organs or whether it serves some function there under these conditions cannot be stated It is interesting to speculate concerning the latter possib[illegible] Since during infection the over all metabolism of the tissues

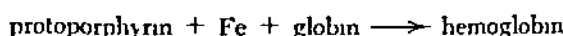
is markedly increased and iron porphyrin enzymes such as the cytochromes myoglobin catalase and verdoperoxidase are all concerned with cellular respiration it is possible that iron is functioning to an increased extent in these systems Although it seems unlikely that the iron requirement of these enzymes would be great enough to account for the marked alteration in iron metabolism under these conditions Drabkin (39) has recently presented evidence that the rate of "turn over" of cytochrome C in the liver is appreciably higher than the normal rate of hemoglobin "turnover" Another possibility to consider is that iron may function in some manner in the defense mechanism of the body This hypothesis is suggested by the observation that the parenteral administration of iron prolongs the survival time of animals with experimentally induced diphtheria (65 174) Also of possible interest may be the observation of Shorr and associates (94 140) that ferritin possesses vasodepressor activity The recent observation of Lawrence (64) that the "turnover rate" of radioactive iron in the plasma of patients with infections is increased rather than decreased may lend support to the concept that the iron in the liver and spleen under these conditions is functioning actively rather than simply being passively stored

The important question whether hypoferremia is the cause of the anemia or the result or whether the two abnormalities are unrelated may be considered Concerning the first of these possibilities it can be stated that since the parenteral administration of large quantities of iron fails to alleviate the anemia it is unlikely that it is due to an insufficient amount of iron circulating through the bone marrow The second possibility—that the hypoferremia is the consequence of decreased hemoglobin production—does not explain the alterations in iron metabolism since in such conditions as pernicious anemia aplastic anemia Mediterranean anemia and anemia due to protein deficiency hypoferremia does not occur (20 30) In the first three of these conditions the plasma iron level is frequently elevated Therefore by deductive reasoning at least it seems possible that the disturbances in iron metabolism may be more directly related to the reaction to inflammation than to hemoglobin synthesis This is admittedly speculative

Finally the cause of the anemia must be considered As has been discussed already further work is needed before it can be conclusively stated that increased hemolysis is not a factor in the pathogenesis of this anemia However the limited amount of evidence presented to date indicates that the rate of erythrocyte destruction is not abnormal

On the other hand the decreased rate of incorporation of intravenously injected radioiron into hemoglobin together with the bone marrow studies of Hemmeler (64) indicating a "maturation arrest in erythropoiesis at the basophilic normoblast stage strongly suggest that the anemia is the result of decreased bone marrow function The question then arises as to the nature of this defect in erythropoiesis

It has been pointed out that the amount of free protoporphyrin in the erythrocytes is increased This would seem to indicate that the synthesis of hemoglobin up to the stage of protoporphyrin is adequate Since hemoglobin synthesis is reduced it is likely that there is a defect in the reaction



protoporphyrin + Fe + globin ⟶ hemoglobin

Thus the defect may lie either in the insertion of iron into the porphyrin *molecule or in the synthesis of globin The evidence that iron* metabolism is in other respects greatly altered might be construed as evidence in favor of the view that there is a defect in the synthesis of heme from protoporphyrin The several similarities between iron deficiency anemia and the anemia of infection might also suggest this On the other hand there is evidence of altered protein metabolism in patients with infections as indicated by a negative nitrogen balance and numerous changes in the plasma protein pattern One would wonder therefore about the possibility that the fundamental defect is in globin synthesis Somewhat contradicting this possibility is the observation that swine made severely protein deficient and anemic do not develop hypoferremia hypercupremia or an increase in erythrocyte protoporphyrin (30) However dietary protein restriction and altered protein metabolism in infection may be quite different Additional studies will be necessary before the defect in erythropoiesis in the presence of infection can be defined more precisely The possibility that the primary defect is not in hemoglobin synthesis but rather in red cell stroma formation cannot be overlooked Of this possibility however very little can be said

It is generally thought that the mild anemia which accompanies infections is an undesirable and unfortunate consequence of the effects of infection on the body The possibility must also be considered that the anemia represents a physiologic compensatory reaction initiated by the defense activities of the body It does not seem unreasonable to postulate that during infection there are demands on the body which are more important than the maintenance of normal erythrocyte

levels and that erythropoiesis is simply reduced to say a 70 per cent level so that these more important activities may be carried out The observation that the anemia is not progressive but rather is self limited in severity would seem to support this postulate Thus like the compensatory reduction in muscular activity which occurs the anemia may be a compensatory defensive and functional response to a destructive force rather than a detrimental consequence of the action of such a force

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Gout, a Derangement of Purine Metabolism*

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If gout be due to an inborn error of metabolism such as here is suggested it cannot be looked upon as due like other such errors to a rare mutation which occasionally occurs *de novo* but rather as based upon an alternative and slightly divergent path of metabolism met with in a large part of the total population A E Garrod *The Inborn Factors in Disease*

GOUT may be defined as basically a derangement of purine metabolism ordinarily identifiable by the presence of "essential hyperuricemia When clinically overt it is characterized by typical recurrent attacks of acute arthritis eventually also by urate deposits often particularly manifest in and around the joints of the extremities The natural history of gout is conveniently divided into four phases (*1*) asymptomatic essential hyperuricemia (*2*) acute gouty arthritis (*3*) intercritical gout (*4*) chronic tophaceous gout This division admittedly is arbitrary and subject to frequent overlapping but it serves to identify more or less distinct clinical aspects of the disease which present quite different problems in management The classification also implies the operation of several different mechanisms within the framework of the underlying basic error in metabolism

The authors laboratory studies included in this report were supported in part by a grant from the National Institute of Arthritis and Metabolic Diseases National Institutes of Health and from the John A Hartford Foundation

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in an analysis of 201 members of 44 gouty families A striking example of familial hyperuricemia from our own experience is shown in Figure 1 illustrating the inheritance of the trait in homozygote strains

It is evident that in these families "essential" hyperuricemia is indeed an inborn error of metabolism Genetic analysis indicates inheritance as a single dominant trait with incomplete penetrance and that the transmitting gene is autosomal not sex linked (172 180) Only a minority of the genetic carriers of the metabolic derangement underlying gout present recognizable manifestations of the disorder This is particularly true of women who constitute a substantial proportion of

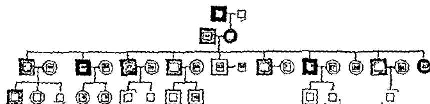


Fig 1 --Genealogy of family R showing transmission of the gouty trait in a homozygotic strain Solid squares males with overt gout hatched squares males with hyperuricemia (serum urate greater than 6 5 mg /100 cc) but no overt symptoms hollow squares males free from hyperuricemia and symptomatic gout Hatched circles females with hyperuricemia (serum urate over 5 5 mg /100 cc) but no overt gouty symptoms hollow circles females free from hyperuricemia and symptomatic gout Broken squares and circles family members not examined Numbers signify age of subject

subjects with unequivocal essential hyperuricemia (although the stigma appears later in life and is generally less pronounced than in men) but who make up only some 5 per cent of patients with manifest gout In men the trait first expresses itself as essential hyperuricemia usually after puberty (172 173) and as gouty arthritis if at all ordinarily in middle age The significance of these striking sex differences remains obscure--why gouty arthritis develops in proportionately few women with an evident genetic predisposition to gout and why it is that serum urate levels in "essential hyperuricemia tend to be somewhat lower in women than in men

The sex difference in respect to serum urate levels may be a reflection or exaggeration of the similar (and also unexplained) differences obtaining normally In our own studies (220) employing a method incorporating the use of uricase (43) the mean serum urate level was found to be 5 4±1 4 and 4 1±0 9 mg per 100 cc in 56 normal men and

NATURAL HISTORY OF GOUT

ESSENTIAL HYPERURICEMIA AS SOLE MANIFESTATION OF GOUTY TRAIT It is becoming increasingly apparent that the disorder of purine metabolism characterizing gout is more common than is generally realized But usually it is of such minor degree as never in the lifetime of the subject to cause clinically recognizable manifestations The one identifying stigma of the disease in such persons is hyperuricemia not attributable to nonprotein nitrogen retention or to such causes of hyperuricemia as polycythemia leukemia or multiple myeloma It is probable that with minimal degrees of the metabolic abnormality even this hallmark of the gouty trait may be absent since the generally accepted upper limits of the normal serum urate are quite arbitrary particularly for women and do not take into account increases within the normal range moreover unequivocal hyperuricemia may be intermittent in some subjects hence easily missed and the urinary clearance of urate may well be sufficient to compensate for significant overproduction of urate in some instances

The clearest indication of the frequency of "essential hyperuricemia as the sole manifestation of the gouty trait comes from systematic surveys of the asymptomatic blood relatives of subjects showing overt gout That gouty arthritis has a distinct familial incidence was known to the earliest students of the disease English observers have variously estimated the familial incidence of overt gout as 38 to 81 per cent in their cases American clinicians dealing with a more heterogeneous population have reported lower figures varying from 6 to 18 per cent in different series (147) The incidence of asymptomatic genetic carriers of the gouty trait was not revealed however until the studies of Jacobson (117) and Talbott (189) appeared Talbott found that 25 per cent of 136 symptom free blood relatives of 27 index patients with manifest gout had serum urate levels exceeding 6 mg per 100 cc in 20 of these 27 families at least one member in addition to the index patient had hyperuricemia Smyth *et al* (172) examined 87 symptom free blood relatives of 19 index patients with clinically overt gout and found that in 11 of the 19 families represented hyperuricemia was present in at least one member other than the index patient Of 48 male relatives 13 had serum urate levels of 6 mg per 100 cc or more of 39 female relatives 11 had levels of 5 mg per 100 cc or more—28 per cent of the 87 family members therefore showed asymptomatic hyperuricemia Comparable findings were reported also by Stecher *et al* (180)

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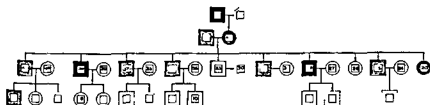


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subjects with unequivocal essential" hyperuricemia (although the stigma appears later in life and is generally less pronounced than in men) but who make up only some 5 per cent of patients with manifest gout In men the trait first expresses itself as "essential hyperuricemia usually after puberty (172 173) and as gouty arthritis if at all ordinarily in middle age The significance of these striking sex differences remains obscure—why gouty arthritis develops in proportionately few women with an evident genetic predisposition to gout and why it is that serum urate levels in "essential hyperuricemia tend to be somewhat lower in women than in men

The sex difference in respect to serum urate levels may be a reflection or exaggeration of the similar (and also unexplained) differences obtaining normally In our own studies (220) employing a method incorporating the use of uricase (43) the mean serum urate level was found to be 5 4±1 4 and 4 1±0 9 mg per 100 cc in 56 normal men and

51 normal women respectively These figures agree closely with the data of Wolfson *et al* (213) There appears to be a relation between the serum urate level and body build Thus Gertler *et al* (89) in studies limited to men found the mean serum urate normally to be significantly higher in dominant endomorphs than in mesomorphs or ectomorphs We have ourselves noted a significant correlation between serum urate level and body surface area in normal men r=0 427 P=0 001 but in normal women r=0 187 P>0 1

These observations raise the question whether the serum urate level may be related to and perhaps in part be derived from the muscle mass a relation less apparent from the body weight or surface area in women because of the large and varying body fat content (183) There are indications of the extrahepatic origin of some urate (29) specifically from muscle and bone marrow (46 47) Such a possibility might throw some light upon the sex differences in respect to serum *urate concentration and incidence of gout and upon the propensity of* gout to attack heavy set men

Although genetic analysis clearly discloses the hereditary characteristics of essential hyperuricemia it does not indicate whether the fault transmitted determines a variant in purine metabolism leading to over production of urate or a peculiarity of renal function favoring urate retention There is strong evidence supporting the former view

Acute Gouty Arthritis Acute attacks of gout rarely occur in the absence of hyperuricemia and then in significant incidence only in the presence of the underlying more or less specific metabolic derangement reflected by what is here referred to as essential hyperuricemia A possible exception is hyperuricemia associated with polycythemia vera in which incidences of acute gout of 5 and 9 per cent have been reported (200 201) Which few of the population with asymptomatic essential hyperuricemia will develop the overt manifestations of gout and when cannot be predicted probably not even on the basis of the degree of elevation of serum urate although those with sustained very high levels may well show a greater mean incidence Presumably it is not the hyperuricemia in itself that elicits the acute gouty attack which is touched off by obscure mechanisms superimposed upon the underlying metabolic disorder The general experience is that male sex marked familial incidence of manifest gout pyknic habitus dietary and alcoholic overindulgence and advancing years weight the probability of overt symptoms and that trauma infections surgical procedures and emotional upsets are common precipitating causes Season and climate

also appear to play a role How these several factors operate to incite an acute attack cannot now be discerned

As to the attack itself the classic description by Sydenham (187) is best cited

> He goes to bed and sleeps well but about two a Clock in the Morning is waked by the Pain seizing either his great Toe the Heel the Calf of the Leg or the Ancle this Pain is like that of dislocated Bones with the Sense as it were of Water almost cold poured upon the membranes of the parts affected presently shivering and shaking follow with a feverish Disposition the Pain is first gentle but increases by degrees sometimes resembling a violent stretching or tearing those Ligaments sometimes the gnawing of a Dog and sometimes a weight moreover the part affected has such a quick and exquisite Pain that it is not able to bear the weight of the Cloths upon it nor hard walking in the chamber and the Night is not passed over in Pain upon this account only but also by reason of the restless turning of the part hither and thither and the continual Change of its place yet there is no ease to be had till two or three a Clock in the Morning And now being in a breathing Sweat he falls asleep when he wakes he finds the Pain much abated and the Part affected swelled afresh for before that there was only (which is usual in the Fits of those that have the Gout) visible a swelling of the Veins intermixed with the affected Members The next Day and perhaps two or three after the part affected will be in Pain which will be violent towards Evening but it will be eased about the time of the Cocks crowing within a few Days the other Foot will be in Pain as the former was and if the former have left off aking the Weakness which rendered it infirm will presently vanish Strength and perfect Health being so presently restored as if it never had been out of order

The classic full blown attack of acute gouty arthritis then includes both local and constitutional manifestations of inflammation swelling redness heat and exquisite tenderness of the involved area which in the majority of instances is the metatarsophalangeal joint of the great toe but may be the other small joints of the foot the ankle heel knee (or prepatellar bursa) elbow (or olecranon bursa) or small joints of the hand or wrist excruciating pain depression gastrointestinal discomfort fever leukocytosis and increased erythrocyte sedimentation rate There often is some premonitory indication of an impending attack usually twinges of pain or stiffness in the affected joint The initial seizure in the majority of instances is limited to a single joint ordinarily of the foot At first this area is apt to be the preferred site of subsequent attacks but later there may be progressive involvement of the other joints of predilection which flare up successively as the preceding affection subsides or initiate a new cycle of migratory arthritis Incapacitation for days or weeks is the rule if appropriate treatment is not

instituted promptly and discomfort on weight bearing or pressure may persist even longer Complete restitution of the affected joint to normal *is characteristic of acute gouty arthritis in the earlier phases of the disease*

There are varying degrees of intensity and duration of acute gouty attacks some apparently consisting of no more than transitory pain or stiffness Such episodes are often difficult to evaluate since the apprehensive gouty patient is prone to ascribe a variety of complaints articular and visceral to his gout

Intercritical Gout With subsidence of the initial attack of acute gouty arthritis and complete restitution of the affected joint the patient to all external appearances resumes his prior status of asymptomatic essential hyperuricemia *As a rule the course thereafter is different* The first attack indicates that the underlying metabolic disorder will sooner or later again become clinically overt as a recurrence of acute gouty arthritis and perhaps also as manifest tophaceous gout Once an acute attack has occurred the probability of progressive disease is greatly enhanced though the patient may for a time be completely free of complaints This likelihood should be taken into account in the management of gout

Usually an intercritical period of several years elapses before the second seizure occurs in many instances this spacing of attacks continues throughout life with only sporadic episodes of acute gouty arthritis separated by completely symptom free intervals of long duration In more severe untreated cases however there is a gradual and progressive shortening of the intercritical periods so that eventually the patient has a respite of only a few months between attacks Moreover with the passage of time and the repeated involvement of the joints the acute attacks are apt to leave more and more residual stiffness swelling and tenderness in their wake and thus the intercritical periods merge imperceptibly into the stage of chronic tophaceous gout with continuous discomfort and disability

Prediction at the time of the first attack is hazardous In general however the course of the disease is likely to be more rapidly progressive and extensive if the onset occurs relatively early in life and is of fulminating character with multiple joint involvement and early recurrence

Chronic Tophaceous Gout Whereas the dramatic occurrence of acute gouty arthritis has attracted attention from the earliest times the deformities and disabilities of chronic tophaceous gout appear so in

sidiously that they receive comparatively little notice even from the patient except in the more advanced stages Fortunately crippling tophaceous joint involvement is the exception but intermediate grades of disability occur frequently enough to be a major hazard of the disease

When urate is formed in the body at a greater rate than it can be disposed of it is deposited in the tissues particularly in cartilage synovial membranes bursae ligaments tendons subcutaneous tissue skin kidneys and scleras The precipitated urate crystals act as foreign bodies inciting characteristic inflammatory responses in the tissues and encroaching particularly upon articular structures to cause pressure atrophy and other degenerative changes (8 37 126 151) Deposits that are sufficiently close to the body surface to be evident upon superficial inspection are recognizable as tophi If they happen to impinge closely enough upon bony structures to cause distinct erosions they may be localized roentgenographically as the more or less typical punched-out areas identified with gout However it is becoming increasingly apparent that neither visual nor roentgenographic evidence adequately indicates the incidence or extent of uric acid infiltration in patients with chronic gout

Several lines of investigation point in this direction The most direct is examination of the tissues post mortem or after amputation of a tophaceous extremity which often discloses previously unsuspected sites of urate deposit and sometimes reveals extraordinary displacement and invasion of normal tissues by grumous urate material (8 37 126 151) Another line of evidence derives from estimation of the miscible pool of urate i e the quantity of urate present in the body capable of prompt mixing with intravenously injected uric acid (10) In the normal male the miscible pool of urate comprises some 1 2 Gm (10 88 192) In gouty subjects the quantity is markedly increased (10 11 182 192) about thirty fold in one instance of advanced tophaceous gout of many years duration Of special interest in this connection is a study by Stetten and associates (10) of a man who had had only two attacks of gout was entirely free of symptoms during the period of study and was without demonstrable tophi His miscible pool of urate nevertheless was approximately 4 8 Gm or about four times the normal quantity Depositions of substantial quantities of urate were thus demonstrated These at the time caused no complaints and were not evident upon ordinary clinical or roentgenographic examination

The significance of these findings may become more apparent if the

method for estimating the miscible pool of uric acid and of the nature of the pool is described

When a known quantity of N^{15} labeled uric acid is injected intravenously it rapidly mixes with and is diluted by a volume of unlabeled urate already present in the circulating fluids and the tissues just as injected T 1824 dye will mix with and be diluted by the circulating plasma It is not convenient to determine the degree of dilution of the N^{15} labeled urate in plasma however this is best accomplished in the larger and more accessible quantities excreted in the urine If the N^{15} concentration of the uric acid excreted on successive days is plotted against time on semilogarithmic coordinates a straight line is obtained (10) whose slope of decay is equivalent to the proportion of the miscible pool replaced daily by newly formed uric acid in the normal subject this quantity is found to be of the order of 750±100 mg or some 60 per cent of the miscible pool (10 182) From the extrapolated intercept (the logarithm of the excess N^{15} concentration of the miscible pool at the time of initial mixing) and the quantity and isotope concentration of the injected N^{15} labeled uric acid the magnitude of the miscible pool can be calculated The turnover rate of the pool is computed from the quantity of the miscible pool and the slope of the line of decay

In normal subjects the state of dispersion and the accessibility of the body urate may well be such that the injected N^{15} labeled uric acid is rapidly and uniformly diluted and the miscible pool presumably approximates the quantity of urate actually present in the circulating fluids and the tissues In chronic gout however particularly in patients with extensive large tophi the morphologic limits of the miscible pool are ill defined Admixture of the injected N^{15} labeled uric acid with the body urate in the solid phase is very incomplete (10 182) In these circumstances the miscible pool even if markedly increased represents only a fraction of the quantity of urate actually stored in the body

A third indication that appreciable amounts of urate may be retained by gouty subjects without clinical or roentgenologic evidence of tophi is provided by quantifying the excess urinary excretion produced by uricosuric agents (103 219) If such agents are administered to normal subjects on a constant low purine low protein diet a distinct uricosuric effect is obtained for only a few days and the total amount of urate excreted in excess of that corresponding to the control period preceding medication is of the order of 1 0 Gm This figure is of the same order of magnitude as the estimated 1 2 Gm for the miscible urate pool al though the body water is not of course wholly depleted of its urate content In patients with gout pronounced uricosuria is maintained usually for weeks or months even on a constant low purine low pro tein intake and the total excess mobilizable urate is as a rule greatly

increased In one of our cases of advanced tophaceous gout it was as high as 90 Gm over a 6 month period Even in chronically gouty patients without visible tophi the total excess mobilizable urate usually is significantly enhanced of the order of 3 to 10 Gm or more This method obviously gives only crude estimates of the amount of urate stored in the body However the results emphasize again the inadequacy of ordinary clinical and roentgenographic estimations of the incidence and extent of urate deposits in gouty subjects

In a survey of the literature McCracken *et al* (141) found that in



Fig 2 —Chronic tophaceous gout tophi on ear

750 reported cases of gout 45 7 per cent of the patients had visible subcutaneous tophi If this figure be taken as a minimal indication of the incidence of appreciable urate retention it becomes apparent that in chronic gout there is a quite general disposition to store varying quantities of urate in the tissues This disposition presumably accentuated by associated impairment of renal function should be taken into account in management even though the amount of urate retained in most instances appears to be inconsequential in terms of overt disability

It follows that the term chronic tophaceous gout" properly applies to long standing cases even in the absence of visible tophi Common usage however restricts the designation to those patients showing

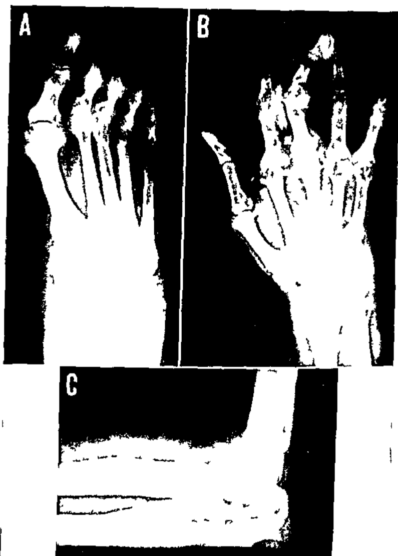


Fig 5 —Roentgenograms in chronic tophaceous gout A characteristic punched out areas of first metatarsal bone of foot B extensive destruction of bones of hand by tophaceous deposits C Large urate deposits in olecranon bursa with cystlike destruction of proximal end of ulna

Appreciable deposits of urate are often discovered in the kidneys at autopsy particularly in the collecting tubules of the medulla but may not be conspicuous Moderate or severe nephrosclerosis is apt to be the presenting finding together with a significant incidence of pyelo nephritis associated with tubular blockade by urates (39)

Urate calculi in the ureters occur in 10 to 15 per cent of patients

ORIGINS OF URIC ACID IN MAN

There appear to be at least three metabolic pathways for the production of uric acid in man (*1*) Degradation of ingested preformed nucleoproteins and nucleotides from exogenous sources (*2*) degradation of endogenous nucleic acids synthesized in the body (*3*) direct biosynthesis from simple carbon and nitrogen compounds without intermediary formation of nucleic acids Probably all three pathways are significant in relation to gout The first dependent on dietary intake may overload the gouty subject s capacity to metabolize intermediate purine compounds and to excrete the difficultly soluble ultimate prod uct uric acid particularly if renal function is impaired The second may have the same consequences if the turnover of nucleic acids is unduly accelerated as presumably occurs in polycythemia vera and other blood dyscrasias and may be even more directly associated with essential hyperuricemia in gout The third pathway is of special in terest in regard to the overproduction of urate

Uric Acid from Ingested Preformed Nucleoproteins and Nucleotides Preformed purines are ingested chiefly as nucleoproteins and nucleotides important constituents of all common foodstuffs par ticularly those rich in cellular elements The nucleoproteins are com pounds of nucleic acids and proteins and combine all the complexities and varieties of structure of both categories of substances (54 64 65 100 128 163) Hydrolysis of nucleic acids yields adenine and guanine aminopurines which are important precursors of uric acid pyrimidines including cytosine uracil and thymine which are metabolized to urea and do not contribute to uric acid formation pentose or desoxypentose and phosphoric acid Nucleic acids derived from cytoplasm are pre dominantly pentosenucleic acids (PNA) often referred to as ribonu cleic acids since the pentose thus far identified is D ribose Nucleic acids derived from nuclei are characterized for the most part by the presence of D 2 desoxyribose hence are designated desoxyribonucleic acids or desoxypentosenucleic acids (DNA) Both PNA and DNA are high polymer compounds notably the latter with molecular weight of 1 000 000 or more

NUCLEOPROTEINS —p p in (stomach)→ NUCLEINS —tryp in (small int tine)→ NUCLEIC ACIDS —ribo and de oxyrib nucleas s (small intestine)→ OLIGONUCLEOTIDES → MONO NUCLEOTIDES

HYPOXANTHINE PHOSPHORIBOSIDE (INOSINIC ACID) —phosphatas (small int tine)→ HYPOXANTHINE RIBOSIDE (INOSINE) —ribo n cleo ide ph phoryla e→ HYPOXANTHINE —xanthine oxida e→ XANTHINE —xanthine oxida e→ URIC ACID

ad nylic a id deamina e (small int tine) ↑

ad no ine deaminas (small int stine) ↑

ADENINE PHOSPHORIBOSIDE (ADENYLIC ACID) —phosphatas (small int tine)→ ADENINE RIBOSIDE (ADENOSINE)

GUANINE PHOSPHORIBOSIDE (GUANYLIC ACID) —pho phata e (small intestine)→ GUANINE RIBOSIDE (GUANOSINE) —ribose nucleoside phosphorylas→ GUANINE —guanase→ XANTHINE —xanthine oxid s→ URIC ACID

ADENINE PHOSPHODESOXYRIBOSIDE —pho phata (mall inte tine)→ ADENINE DESOXYRIBOSIDE —deamina e and de oxyribos n leo ide ph phoryla e→ HYPOXANTHINE —xanthine oxida e→ XANTHINE —xanthine oxidase→ URIC ACID

GUANINE PHOSPHODESOXYRIBOSIDE —pho phata (small i t tine)→ GUANINE DESOXYRIBOSIDE —d oxyribo nucleo ide phosphorylas→ GUANINE —guana→ XANTHINE —xanthine oxidas→ URIC ACID

Fig 6 —Schematic representation of the degradation of ingested preformed *nucleoproteins* *Top line represents the steps* leading to formation of the mononucleotides Remaining lines indicate main pathways of conversion of the principal purine phosphoribosides and phosphodesoxyribosides to uric acid

Nucleotides are widely distributed in cells for example as coenzyme nucleotides but in very small amount Adenosine triphosphate (ATP) however occurs in muscle to the extent of about 2 5 mg per gram of muscle according to Szent Gyorgyi (188) Its degradation products along with those of other nucleotides present might be a significant source of urate after meals are eaten that contain large amounts of meat

The degradation of ingested nucleoproteins involves a number of steps each requiring separate enzyme systems (Fig 6) In the stomach they are acted upon by pepsin to form nucleins protein–nucleic acid complexes of variable composition Further hydrolysis by trypsin in the small intestine completes the separation of the protein moiety leaving the nucleic acids in the form of macromolecular complexes These are then depolymerized by ribo and desoxyribonucleases of the small intestine to oligonucleotides (pentose and desoxypentose nucleic acids of low molecular weight) possibly of the classic tetranucleotide structure, which are further degraded to the mononucleotides adenylic acid guanylic acid and the corresponding desoxyribose nucleotides Some nucleotides may be absorbed as such some may be deaminated in the small intestine prior to dephosphorylation for example adenylic acid may be deaminated by adenylic acid deaminase to inosinic acid But most of the ribose and desoxyribose nucleotides probably are first dephosphorylated by the alkaline phosphatases of the intestine to the corresponding purine ribosides and desoxyribosides Adenosine is deaminated by adenosine deaminase of the intestinal mucosa to inosine The next step is conversion of the nucleosides inosine and guanosine (and their desoxyriboside equivalents) to hypoxanthine and guanine, respectively by purine "nucleosidases" This actually involves phosphorolysis by specific ribose and desoxyribose nucleoside phosphorylases as Kalckar (120) and Friedkin and Kalckar (77) have shown ribose 1 phosphate (or desoxyribose 1 phosphate) is thereby formed Hypoxanthine is then oxidized in the No 2 carbon position by xanthine oxidase to xanthine guanine is deaminated in the No 2 carbon position by guanase to xanthine and xanthine is oxidized in the No 8 carbon position by xanthine oxidase to uric acid In most mammals uric acid is further degraded by uricase to allantoin but human tissues appear to be devoid of uricase and the chief purine end product of nucleic acid catabolism in man is uric acid In the bird and reptile uric acid is the chief final product of all nitrogen metabolism—proteins as well as nucleic acids

Uric Acid from Endogenous Nucleic Acids Synthesized in Body
Little is known about the pathways of biosynthesis of the nucleic acids or of the intracellular breakdown of nucleic acids leading to conversion of the incorporated purines—adenine and guanine—to uric acid However work utilizing N^{15} and C^{14} as tracers which is still in active progress gives some clues to the nature of the over all reactions

It has long been known that man can be maintained without weight loss or other detriment on a diet low in purines and that he will continue to excrete 0 3 to 0 5 Gm of uric acid per 24 hours in the urine (endogenous urate) under these conditions Such clear evidence of uric acid formation from nonpurine precursors notably ammonia (31) was generally interpreted as also implying biosynthesis of nucleoproteins which as they are catabolized yield this quantity of endogenous uric acid The precursors of nucleic acid were not further identified however until Barnes and Schoenheimer (5) showed that the nitrogen of ingested N^{15} labeled ammonium citrate was rapidly incorporated into the guanine and adenine of the tissue nucleic acids of the pigeon and rat indicating purine synthesis from the general body nitrogen pool derived from dietary amino acids the uric acid of the pigeons or the allantoin of the rats collected in these experiments also contained a significant concentration of N^{15} Plentl and Schoenheimer (150) then made the surprising observation that the N^{15} of ingested labeled guanine appeared almost exclusively in the allantoin or uric acid excreted by the rat or pigeon none being found in the purines (including guanine) or pyrimidines isolated from nucleic acid From this they inferred that the preformed purines of the diet are not utilized for synthesis of nucleoproteins Brown *et al* (38) confirmed these findings about the fate of dietary guanine but found that N^{15} labeled adenine in contrast to guanine is utilized for formation of both adenine and guanine of the nucleic acids of the rat and N^{15} appears in significant concentration in the excreted allantoin In adult rats the N^{15} of ingested labeled adenine is incorporated almost exclusively into PNA purines very little appearing in DNA fractions except in rapidly growing tissue such as regenerating liver (83) It has since been shown by several groups of investigators however that phosphorus the nitrogen of glycine β carbon of serine methylene carbon of glycine and carbon of formate are all incorporated at a significant rate into DNA in the adult animal indicating that continuous biosynthesis of DNA from these compounds takes place evidently by a different mechanism from that utilized in the slow incorporation of adenine

(84) The fact that glycine serine and formate also are utilized for more direct pathways of uric acid synthesis not involving prior formation of nucleic acids suggests elaboration of a common purine intermediate which can then be used either for synthesis of nucleic acid purines or may be oxidized directly to uric acid (140) Indications of the nature of this common intermediate are already at hand

The rate of formation of uric acid from the adenine and guanine of nucleic acids depends largely on the turnover rate of PNA and DNA Ordinarily the turnover rate of PNA greatly exceeds that of DNA (83 106) and the purine bases of PNA therefore presumably contribute a much larger proportion of the uric acid formed However it may be inferred that the turnover rate of nuclear DNA is greatly accelerated in such conditions as polycythemia vera leukemia multiple myeloma and in pernicious anemia following administration of liver extract in these conditions hyperuricemia and even overt gout may occur and a substantial proportion of uric acid production may derive from DNA

Direct Biosynthesis of Uric Acid One of the most elegant accomplishments of the application of isotope tracer methods to the study of metabolism is the identification of simple carbon and nitrogen precursors of uric acid the precise localization in the uric acid molecule of each precursor and the recognition of previously unsuspected biosynthetic pathways Barnes and Schoenheimer (5) by their discovery in 1943 that dietary ammonia nitrogen is readily incorporated into the uric acid and allantoin excreted by the pigeon and rat respectively made the first contribution Three years later Buchanan and associates (44 176) reported the first of a series of brilliant studies in this field Using C^{13} labeled compounds as tracers in the pigeon they found that carbon atoms nos 4 and 5 of the uric acid molecule are derived from glycine carbon atom no 6 from carbon dioxide and the ureide carbons nos 2 and 8 from formate Shemin and Rittenberg (167) fed N^{15} labeled glycine to a normal human subject and noted rapid incorporation of the glycine nitrogen into position 7 of the excreted uric acid with lesser and slower utilization in positions 1+3 and 9 presumably by way of the general nitrogen pool From the subsequent work of a number of investigators (45 71 122 177) the following conclusions may be drawn (1) Dietary ammonia nitrogen is readily incorporated into positions 1 3 and 9 of the uric acid molecule directly or by way of the general nitrogen pool (2) Glycine chiefly contributes carbon atoms nos 4 and 5 and nitrogen atom no 7 to the formation of uric acid small amounts of nitrogen also appear slowly in positions 1

3 and 9 presumably via the general nitrogen pool the ureide carbon atoms nos 2 and 8 may also arise from glycine Formate derived from the α carbon of glycine the β carbon of serine or other sources is the immediate source of ureide carbon atoms nos 2 and 8 Since serine is readily (and reversibly) converted to glycine and formate it too must be regarded as a direct precursor of uric acid Carbon atom no 6 of the uric acid molecule is derived by fixation of carbon dioxide

The over all pathway of biosynthesis is indicated in Figure 7 in

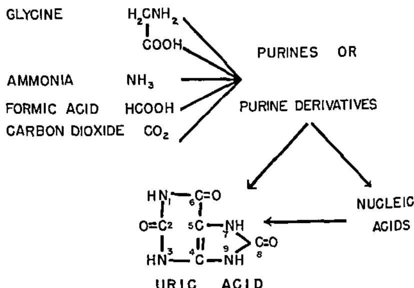


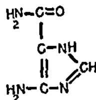
Fig 7 —Precursors in biosynthesis of uric acid The metabolic pathways may include intermediate formation of nucleic acids but as indicated this is not an obligatory step

which it is shown that uric acid may be elaborated without obligatory prior formation of nucleic acids This direct synthesis was fore shadowed by Plentl and Schoenheimer when they found that the nitrogen of ingested N^{15} labeled guanine appeared in the allantoin or uric acid excreted by the pigeon and rat respectively but not in the nucleic acid purines or pyrimidines Subsequent work by many investi gators leaves no doubt concerning an alternative direct route of syn thesis Indeed possible intermediates have been identified and path ways of synthesis suggested

Stetten and Fox (181) isolated a new amine from cultures of Escherichia coli subjected to bacteriostasis by sulfonamides and Shive

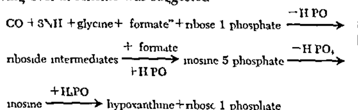
et al (168) showed that this substance was 5(4)—amino—4(5) imidazole carboxamide (Fig 8) Since this compound has the structure of a purine except for the absence of a carbon atom in position 2 Shive *et al* suggested that it might be a purine precursor The evidence as to the place of 5(4) amino-4(5) imidazole carboxamide in purine synthesis is still conflicting but there is strong indication that either the carboxamide itself or a derivative is a key intermediate For example Schulman and Buchanan (161 165) were able to show that when 5(4) amino 4(5) imidazole carboxamide and formate are incubated with pigeon liver homogenate they combine approximately in mol for mol proportions to form hypoxanthine The reaction goes no

Fig 8—Structural formula of 5(4) amino-4(5) imidazole carboxamide probable intermediate in the biosynthesis of purines



further than hypoxanthine formation pigeon liver lacking xanthine oxidase but ordinarily hypoxanthine could be oxidized to xanthine and then to uric acid by this enzyme It has also been shown that 4(5) amino 5(4) imidazole carboxamide can be converted to adenine and guanine by yeast suspensions

Greenberg s (92 93) work makes it seem likely that in the intermediary reactions leading to direct synthesis of hypoxanthine and ultimately of uric acid ribosides and ribotides (phosphoribosides) are formed before completion of the purine ring Using cell free pigeon liver preparations and differential paper chromatography and spectrophotometry to identify the products successively formed in the presence of ammonia carbon dioxide glycine formate and ribose 1 phosphate Greenberg found that the first purine compound detectable was inosine 5 phosphate Later inosine then hypoxanthine appeared The following overall scheme was suggested



In this scheme the "riboside intermediates may well include the riboside of 4(5) amino 5(4) imidazole carboxamide Greenberg (93)

8 and 9 presumably via the general nitrogen pool the ureide carbon atoms nos 2 and 8 may also arise from glycine Formate derived from the α carbon of glycine the β carbon of serine or other sources is the immediate source of ureide carbon atoms nos 2 and 8 Since serine is readily (and reversibly) converted to glycine and formate it too must be regarded as a direct precursor of uric acid Carbon atom no 6 of the uric acid molecule is derived by fixation of carbon dioxide

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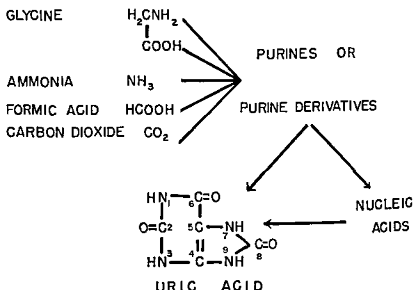


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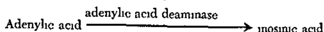
World monkeys appear to lack uricolytic enzymes so that in these species uric acid must be disposed of as such In man urate is disposed of chiefly by way of renal excretion Small quantities normally are also excreted in the gastric and intestinal juices bile, saliva, and sweat These routes are adequate in the healthy state but in gout the body often cannot excrete sufficient urate via these channels and it is deposited in the tissues all the more readily because of the sparing solubility of uric acid and its salts

RENAL EXCRETION OF URATE The mean daily urinary excretion of urate in normal man on a diet low in purines approximates 0 4 Gm To cite more recent reports Brøchner Mortensen (33 35) using his ferricyanide method found a range of 269 to 532 mg per 24 hours (mean 374 mg) in 20 normal persons Friedman and Byers (81) in a study of 6 normal subjects observed a range of 360 to 438 mg per 24 hours (mean 390 mg) Another study using the uricase technic in 13 non gouty subjects on a low purine low protein diet gave a mean of 416 ±68 mg per 24 hours with a range of 308 to 533 mg (220) Despite the rather wide variation in the level of urinary urate excretion observed in normal persons the daily "endogenous" excretion in any one individual is remarkably constant and unaffected by ordinary fluctuations in activity and environment (49) The chief common cause of substantial increase in the urinary urate excretion of normal man is a high dietary intake of purine (170) or protein (74)

Most of the evidence indicates that in man the quantity of urate excreted in the urine represents only a small fraction (normally some 5 to 10 per cent) of that filtered through the glomeruli (14 190) which is estimated to be 5 or 6 mg of urate per minute in normal human subjects of average body surface (14) These figures are based on simultaneous determinations (61 190) of urate clearances (normal mean 7 to 10 cc per minute at adequate urine flows [33 35 61 190]) and glomerular filtration rate as measured by the inulin clearance (normal mean approximately 125 cc per minute corrected to standard body surface) From these data then over 90 per cent of the urate filtered is normally reabsorbed in the tubules Why such a high proportion of a metabolic end product in man should be so carefully reabsorbed is not clear In most mammals urate reabsorption presumably is for the purpose of conversion to allantoin in the liver

It is assumed in these estimates that (*1*) all the plasma urate is in a form filtrable through the glomerular membranes and that the quantity of urate in the glomerular filtrate can therefore be equated to the

found no indication that a significant amount of hypoxanthine was formed by way of nucleic acid purines by this system Nor was adenylic acid a precursor of inosine in this system by the reaction



This does not exclude the possibility that adenylic acid and the adenosine polyphosphates may be significant precursors of uric acid under other circumstances since there is some indication that at least part of the uric acid formed in the body is of extrahepatic origin (29) perhaps arising in muscle (46 47)

Considering all these remarkable advances in our knowledge of purine metabolism and the origins of uric acid it is apparent that the problems of gout must be approached with new perspective While the amount of urate formed in the body depends in part upon the quantity of preformed purines ingested the major portion except after very heavy purine rich meals is synthesized from nonpurine precursors this is evident from the substantial urinary excretion of urate in normal human subjects on a diet low in purines (endogenous urate) These precursors the simplest nitrogen (ammonia glycine) and carbon (glycine formate carbon dioxide) compounds may be derived from any form of protein foodstuff and the carbon fragments in large part also from carbohydrate and fat They are utilized at a lively rate for urate synthesis either by direct pathways or through intermediary formation of nucleic acids

The amount of urate formed in the body then is a function not only of the intake of preformed purines but also of (*1*) the rate of formation of urate precursors from ingested protein carbohydrate and fat 2) the availability of these precursors for urate synthesis (*3*) the rate of biosynthesis of purines from these precursors (*4*) the rate and amount of direct oxidation of purines to urate (*5*) and the turnover rates of PNA and DNA in different cells Of particular significance is the availability of the nitrogen of the general body pool for urate production since this implies an alternative and perhaps competing pathway for utilization of amino acid nitrogen in the synthesis of compounds which might otherwise lead to urea and not to uric acid formation

DISPOSITION OF URIC ACID IN MAN

Whereas in most mammals uric acid is converted by uricase to the more readily soluble allantoin man the anthropoid apes and New

excretion the urate in the urine according to these estimates thus amounts to approximately ~~80 to 60~~ per cent of the total urate formed In gouty subjects with marked renal damage this proportion might well be even lower

URATE EXCRETION VIA GASTROINTESTINAL TRACT Comparatively little attention has been paid to excretory routes for urate other than renal due in part to difficulties in measurement For example it is not feasible to estimate the fecal excretion of urate as has long been known Esch coli and other bacterial inhabitants of the intestinal tract readily oxidize urate presumably by pathways similar to those characterizing an anaerobic soil bacterium Clostridium acidi urici which oxidizes uric acid to ammonia carbon dioxide and acetic acid (4 123) An experiment by Brown *et al* (88) provides an illuminating example of the extent of disappearance of urate in the bowel

When N^{15} labeled uric acid was fed to a normal subject by mouth only 27 per cent could be recovered in the urine as urate whereas 47 per cent of the isotope ingested appeared in the urinary urea and 2 per cent in the urinary ammonia When the same amount of N^{15} labeled uric acid was injected intravenously into the same subject 93 per cent was recovered in the urine as urate and only traces of N^{15} were found to be incorporated into urinary urea and ammonia

Lucke (135) estimated that the total "enterotropic" excretion of urate (*i e* the total excretion into the gastrointestinal tract as determined by direct measurement in the several juices individually collected) normally comprises some 40 to 70 mg per day or 10 to 15 per cent of the urinary urate This quantity was distributed as follows saliva, 6 to 12 mg gastric juice 15 to 20 mg bile and pancreatic juice 20 to 30 mg Lucke further pointed out that excretion of urate through these channels was increased with hyperuricemia and that in gout associated with marked renal damage the "enterotropic" urate might well constitute a more substantial proportion of the total urate excretion

Obviously the urinary urate excretion cannot be taken as a measure of total urate production particularly if renal function is impaired and urate balance studies which necessarily omit fecal excretion are incomplete notably in gouty subjects Yet these factors have commonly been overlooked with a consequent confusion in the literature

DEGRADATION OF URATE IN MAN It is still a moot point whether in man uric acid can or cannot be oxidized to a significant degree apart from breakdown by the bacterial flora of the intestinal tract Incubation of uric acid with a variety of human tissues gives no indication of

product of filtration rate and plasma urate concentration (2) Tubular secretion of urate such as occurs in lower orders (174) does not take place in normal man In regard to the nonfiltrability of plasma urate it has been claimed that 4 to 24 per cent of the urate in plasma normally is bound to protein (3) or is present as nonfiltrable polymeric complexes (209) This is not corroborated by the results of most investigators employing dialysis (53) or ultrafiltration technics (1 8 15 220) and even if correct would not account for the uric acid clearance deficit *i e* the disparity between inulin and urate clearances (15 51) As for tubular secretion of urate in normal man which has been suggested from time to time there is no convincing evidence either for or against excretion of some urate by the tubules in addition to the urate filtered through the glomeruli *It would be difficult by available technics to obtain satis* factory evidence for tubular secretion in the presence of concomitant tubular reabsorption of urate Praetorius and Kirk (152) have recently described an ostensibly normal young man with hypouricemia whose uric acid clearance appears to have exceeded his inulin clearance suggesting tubular secretion

Berliner *et al* (15) by means of constant intravenous infusion of urate have been able to demonstrate that the tubular transport of urate in normal man is of limited capacity the Tm being of the order of 15 mg per minute This finding has two significant connotations (*1*) Tubular reabsorption of urate involves "active transport presumably through enzyme systems as yet undefined and (*2*) the capacity of the transport system is so much greater than the normal demands upon it that it is not the limiting factor for tubular reabsorption of urate in the normal or probably even in the gouty subject (in whom the Tm for urate has not been determined) The factors which actually determine the amount of urate excreted in the urine therefore remain obscure for normal man and even more obscure for the gouty subject

The amount of urate excreted in the urine and the high recovery rate in the urine of parenterally administered urate shows that disposal of urate normally occurs chiefly by way of the kidneys What proportion of the total urate formed in the body is represented by the quantity excreted in the urine however is still a matter of some uncertainty Stetten *et al* (10) after injecting N^{15} labeled uric acid estimated that in 3 normal subjects with mean daily uric acid excretion of 602±12 mg 563±13 mg and 616±24 mg the daily production of urate was 715 693 and 867 mg respectively This would leave a daily surplus of 110 to 250 mg of urate to be disposed of by routes other than renal

done with a sufficiently large dosage of urate nor have the possible oxidation products all been examined However the experiments in man to date (10 11 88) indicate that only traces of N^{15} appear in the urinary urea and ammonia after injection of N^{15} labeled uric acid Such traces are interpreted as either without significance (88) or as originating in the intestinal flora and reabsorbed rather than as due to tissue enzymes of the host (11)

Deposition of Urate in Tissues As a final alternative to excretion and degradation of urate if these are inadequate to the rate of urate production urate is retained in the body and precipitated as characteristic crystals in predisposed tissues In normal man the miscible pool of uric acid is so small that it is more than accounted for on the assumption of uniform distribution in the body water (10) However in chronic gout (10 11 192) and blood dyscrasias associated with hyperuricemia (192) the miscible pool of uric acid is apt to increase and may reach such proportions as to imply deposition in the tissues as a solid phase even if urate deposits are not apparent on clinical or roentgenographic examination

The susceptibility of man to chronic tophaceous gout does not imply a weakness peculiar to human tissues but rather reflects difficulties common to the disposition of all sparingly soluble compounds when they tend to accumulate in the body Thus much the same picture as chronic tophaceous gout is not infrequently encountered in birds particularly in older birds of prey and in other birds artificially maintained on a high protein diet (30) Because uric acid is the chief end product of all nitrogen metabolism in birds they are especially liable to tophaceous urate deposits when there is excessive intake of protein or impairment of renal excretion

There is no ready explanation for the predisposition of urate for cartilage although it is known that cartilage slices soaked in solutions of uric acid will absorb and retain appreciable quantities (42) The predilection of urate deposits for the large bursae and synovial spaces of the extremities may be more easily understood however because of the tendency of other difficultly soluble salts calcium phosphate for example to precipitate out of solution in these areas

NATURE OF METABOLIC ERROR IN GOUT

The foregoing summary of the origins and disposition of uric acid in normal man included many important discoveries which give greater

appreciable uricase or other uricolytic enzyme activity if gross bacterial contamination is avoided Moreover the daily excretion of allantoin in man some 10 to 30 mg is so small as probably to represent ingested allantoin and furthermore appears not to be increased in gout (206)

The question of significant uricolysis in man has arisen chiefly as the result of experiments designed to estimate the extent of recovery of injected uric acid particularly in the urine These experiments have given conflicting results in the hands of different investigators some accounting adequately for the injected urate others not Perhaps the most impressive example of the latter category is the experience of Folin *et al* (75) who recovered from the urine of normal men only 30 to 90 per cent of intravenously injected uric acid (20 mg per kg) It was concluded that a mean of 50 per cent of the uric acid injected was oxidized Even these carefully conducted experiments however are open to other interpretation These workers noted that whereas injected uric acid disappeared rapidly from the blood of the dog in which uric acid is certainly oxidized to allantoin the blood uric acid in man rose strikingly following injection declining slowly over a period of days as the uric acid was excreted If degradation took place at all therefore it proceeded with unexpected slowness

These conflicting results and interpretations persist in connection with experiments dealing with the fate of N^{15} labeled uric acid after injection into human subjects As already indicated Stetten *et al* (10) calculated from data obtained in this way that the daily production of urate in 3 healthy young men some 750 mg was 110 to 250 mg in excess of the urinary urate excretion while some of the surplus presumably was excreted in the feces and sweat it was felt that the disparity indicated catabolic breakdown of a portion of the uric acid Talbott *et al* (32) found that 68 to 76 per cent of N^{15} labeled uric acid injected intravenously into 2 normal subjects was excreted as urate in the urine leaving one third to one fourth to be disposed of by other routes "presumably catabolism" Brown *et al* (88) on the other hand were able to recover 95 per cent of intravenously injected N^{15} labeled uric acid in the urine in 5 days

Recovery experiments particularly those limited to recovery of urate in the urine and that over a brief period obviously leave many uncertainties in interpretation and consequently provide inconclusive evidence of uricolysis in man A more direct approach is to determine the isotope content of degradation products of uric acid after intravenous injection of isotope labeled uric acid This has not yet been

(1) If the overproduction of urate is so great that even if the disposal routes are of normal capacity or indeed respond to the need by increasing their capacity they are inadequate to the load and excess urate therefore persists in the body

(2) If urate production is within the normal range or even low but the capacity for disposal is so reduced that urate is nevertheless retained

(3) If there is both overproduction and reduced excretion of urate

(4) If uricolysis occurs in lesser degree in the gouty than in the normal subject thus permitting retention of urate

These several possibilities bring us to the classic key question of gout Is the excessive urate in the blood and tissues in gout due to overproduction impairment of renal excretion or decreased degradation of urate? It is generally agreed that no definitive answer to this question is yet possible and opinion as to the weight of evidence is still divided For example Talbott (189 191) stoutly defends the overproduction theory Thannhauser (195) is a strong proponent of the primary role of impaired renal function Bauer and Klemperer (8) incline to Thannhauser s opinion with some qualifications Hench (111) is noncommittal

DECREASED DEGRADATION OF URATE To start with the least likely possibility it is improbable that oxidation of urate at a rate less than normal can be the intrinsic metabolic defect in gout or anything more than a minor accessory factor in the causation of chronic tophaceous gout Such an explanation would be based on the presumption that uricolysis represents a significant pathway for disposition of urate in normal man still a controversial point

The experience of Folin *et al* (75) principal exponents of this theory is an example of the inconsistencies inherent in the view that perversion of uricolysis is the basic fault in gout In most cases of gout examined the recovery in the urine of injected uric acid was found to be somewhat lower than the mean for normal subjects a finding which was interpreted as indicating *increased* destruction of urate in gout subnormal urinary excretion of urate in gout being taken despite all limitations of this criterion to mean increased destruction of urate In at least 1 case of unequivocal gout however there was almost complete recovery of injected uric acid (93 5 per cent) suggesting *decreased* destruction of urate It seems evident now that the older recovery experiments were wholly inadequate as a means of estimating the degree of uricolysis particularly under the complex conditions of chronic tophaceous gout

insight than has hitherto been possible into the peculiarities of purine metabolism in gout The disorder will now be considered in the light of these advances The principal question to be re examined is whether the basic abnormality of gout really is an error of purine metabolism and if so what may be its essential nature Such an inquiry must of necessity still involve much speculation

It will be noted that thus far our considerations have centered largely upon uric acid Ever since Wollaston in 1797 reported the presence of uric acid in the chalk stones (tophi) of gouty subjects and particularly since Garrod s discovery in 1848 of hyperuricemia in gout preoccupation with uric acid has dominated speculation upon the causes of gout It has been tacitly assumed that uric acid is somehow responsible for all the various signs and symptoms of gout This cause and effect relationship does not necessarily follow no one would now contend that the manifestations of uremia for example are due to urea retention alone even though this is a constant finding—it is recognized that urea is physiologically inert and that the clinical picture of uremia is due to concomitant retention of other substances as yet unidentified A study of the relation of uric acid to gout may show that an analogous situation obtains

In the case of chronic tophaceous gout such deformities and disabilities as may ensue are plainly due to deposition of sparingly soluble urate in the tissues it is understandable that chronic swellings and discomfort may result from displacement and pressure atrophy of the supporting structures secondary inflammatory reactions irritation of nerves and similar complications incidental to large collections of urate However the assumption that acute gouty arthritis also is due to uric acid as such is unwarranted From all indications uric acid is a virtually inert substance in man quite incapable of producing the dramatic manifestations of acute gout We do not know the immediate causes of acute gouty arthritis but they appear to be different from those of chronic gouty arthritis *These two aspects of gout will therefore be considered as more or less discrete phenomena in the discussion that follows*

Chronic Tophaceous Gout

We shall start with the premise that urate is deposited in the tissues when the rate of urate formation exceeds the rate at which it can be excreted and degraded It follows that urate deposition will occur in the following *circumstances*

dynamics as GFR is difficult because it is impossible to disassociate impairment due to sclerosis of renal arterioles or arteries incidental to the advanced age of many of the gouty subjects studied from that attributable to the gout itself In the case of the latter it is not yet clear which is cause and which effect Of interest in this connection are the observations of Friedman and Byers (81) who found the GFR to be normal in each of 5 young gouty patients (mean age 35 mean GFR as measured by allantoin clearance 121 cc per minute per 1 73 M² body surface) but reduced in 3 older gouty subjects (mean age 68 mean GFR 76 cc per minute per 1 73 M body surface) In any case impairment of renal hemodynamics and discrete renal functions is evidently not a prerequisite to "essential" hyperuricemia or overt gout even of long standing

The distinct possibility remains stressed especially by Thannhauser that gout may be characterized by a specific renal defect an inborn error affecting the kidneys which limits their capacity to excrete urate without necessarily affecting other renal activities If there is a specific renal defect of this kind characteristic of gout it has thus far eluded detection The available data in regard to uric acid clearance normally 7 to 10 cc per minute at adequate urine flows according to most observers indicate little or no significant difference between gouty and nongouty subjects Brøchner Mortensen (34 36) found that in 17 of 20 cases of gout the uric acid clearance was either within normal limits or depressed to not more than 60 per cent of normal the latter cases including many instances with marked reduction in urea and creatinine clearance Talbott *et al* (61 190) likewise observed no significant reduction in the mean urate clearance of 27 gouty subjects as compared with 55 nongouty controls although the urate clearance was less than 7 cc per minute in 7 cases of gout Friedman and Byers (81) also noted normal urate clearances in 6 of 8 cases of gout In fact investigators in this field have uniformly been impressed with the maintenance of essentially normal urate clearance rates in the face of very substantial reductions in GFR and urea clearance in gouty subjects with kidney damage (34 36 61 81 190) evidently at the expense of tubular reabsorption of urate This fact would certainly argue *against an intrinsic* constitutional inferiority of the kidneys of gouty subjects to excrete urate (61) The claim of a specific defect in the capacity of the gouty kidney to concentrate urate (195) has not been confirmed (35 81 137 190)

Perhaps the most telling point made for the *primary role* of the

IMPAIRMENT OF RENAL EXCRETION The gouty kidney has long played an important role in speculations about the causes of gout This is not surprising in view of the frequency of pathologic findings in the kidney in gout the high incidence of overt kidney damage as evidenced by persistent *albuminuria cellular casts and nitrogen retention* in chronic gout and the data indicating urinary urate excretion levels within and sometimes below the normal range Unquestionably the presence of renal damage by limiting the capacity to excrete urate aggravates and accelerates the development of chronic tophaceous gout The only point at issue is whether the renal defect in gout can be regarded as the primary and basic cause either of chronic tophaceous gout or of acute gouty arthritis

If aberrant kidney function is the primary abnormality in gout and a necessary condition to its development some renal defect should be a consistent finding in gouty patients and should be in evidence even in asymptomatic "essential" hyperuricemia This clearly is not the case in respect to the ordinary criteria of kidney damage such as albuminuria cellular casts and nitrogen retention The incidence of albuminuria in overt gout is of the order of 25 to 45 per cent in different series that of nitrogen retention some 10 to 15 per cent (36 141) In asymptomatic essential hyperuricemia the incidence of these findings appears to be very much lower Clinical experience therefore indicates that the common expressions of kidney damage usually are a relatively late accompaniment of essential" hyperuricemia and frequently are not in evidence even when overt gout has been present for many years

More refined tests however reveal a larger proportion of cases with impairment of renal function particularly of glomerular filtration rate (GFR) Talbott *et al* (61 190) found that of 26 patients with gout 9 had substantially normal inulin and creatinine clearances (inulin clearance 130 to 95 cc per minute) 10 showed a distinct reduction (inulin clearance 75 to 60 cc per minute) and 7 had markedly impaired inulin clearances ranging from 58 to 12 cc per minute Of the gouty patients with reduced GFR 5 were also studied in regard to renal plasma flow which was found to be commensurately lowered and tubular excretory capacity ($Tm_{d\ a\ t}$) which also was reduced (190) however insufficient data on these discrete renal functions are available for any general statement Brøchner Mortensen (36) reported urea clearances of less than 60 per cent of the normal mean in 19 of 34 cases of gout

Interpretation of these data on such general aspects of renal hemo

531±177 mg which is significantly higher than the mean of the non gouty control group Analysis of the gout cases revealed that age duration of recognized disease and presence of tophi were not critical factors in relation to the magnitude of urinary urate excretion but that the presence or absence of overt renal damage—nonprotein nitrogen retention albuminuria cellular casts or PSP retention—was significantly correlated Thus in 31 patients without overt renal damage (Fig 9B) the range was 389 to 999 mg of urinary urate per 24 hours with a mean



Fig 9—Distribution of urinary excretion levels in mg/24 hours A in 13 nongouty controls B in 31 gouty subjects without overt renal damage C in 24 gouty subjects with overt renal damage Open circles without tophi solid circles with tophi All subjects were maintained on a low purine restricted protein intake for several days before collection of urine specimens Each point represents the mean of determinations of true urate (uricase technic) in several 24 hour specimens For A mean serum urate 4 4 mg/100 cc (range 3 6 to 5 8 mg) for B 9 4 mg/100 cc (range 7 2 to 12 7 mg) for C 9 6 mg/100 cc (range 7 4 to 12 3 mg)

of 605±172 mg a figure significantly higher than that of the nongouty control group In 24 patients with overt renal damage (Fig 9C) the range was 190 to 751 mg of urinary urate per 24 hours with a mean of 436±142 mg which is very close to that of the nongouty control group

Apparently therefore while in the majority of patients with gout the urinary urate excretion levels are within the normal range and in some are below a significant proportion excrete excessive amounts of urate in the urine while maintained on a low *purine diet* In our own series of 55 patients for example the urinary urate excretion per 24 hours exceeded 620 mg (mean normal 416 mg $+3\sigma$) in 29 per cent of the cases This point has become more evident with the recent shift in emphasis to early cases of gout which are free of overt renal damage

kidneys in the causation of gout is the circumstance that the urinary excretion of urate usually is within and sometimes below the normal endogenous limits of approximately 0 4±0 1 Gm per 24 hours in gouty patients on a low purine diet Close examination of the literature on this point however reveals surprisingly meager data that can be accepted as authentic and while the facts appear to be substantially as stated a more elastic interpretation than that generally made seems to be indicated

Brugsch and Schittenhelm (41) reviewed the data available up to 1907 comprising those on 30 gouty subjects and concluded that the urinary urate excretion was below normal in 43 per cent (0 01 to 0 3 Gm per 24 hours) within low normal limits in 36 per cent (0 3 to 0 4 Gm) and within high normal limits in 21 per cent (0 4 to 0 6 Gm) In these studies uric acid was determined by means of ammoniacal silver or as the copper salt methods which tend to give incomplete recoveries as attested by values of less than 0 1 Gm in some instances Folin *et al* (75) reported results obtained colorimetrically with the phosphotungstate reagent In 6 normal subjects the urinary urate excretion was found to range from 425 to 605 mg per 24 hours in 9 gouty subjects the values were 244 350 352 355 366 425 687 889 and 958 mg per 24 hours Thus in two thirds of the cases the urinary urate excretion fell within or below the low normal range while in one third the values definitely exceeded the upper limits of normal

Brøchner Mortensen (36) using his ferricyanide method found the mean urinary urate excretion of 11 gouty subjects to be 414 mg (range 297 to 680 mg per day) somewhat higher than the mean of 374 mg (range 269 to 532 mg per day) in 20 normal persons Talbott and Coombs (191a) encountered 2 patients with gout who excreted greater than normal amounts of urate Friedman and Byers (81) selected 5 relatively young persons with early gout in order to avoid the complication of renal damage with retention of all nonprotein nitrogen end products of metabolism and found mean urinary urate excretions of 472 575 576 601 and 613 mg per day as compared with a range of 360 to 438 mg per day in 6 normal controls

Our own experience in this connection is summarized in Figure 9 The distribution of results obtained in 13 nongouty controls maintained on a low purine diet is indicated in section A range 360 498 mg urinary urate/24 hours mean 416±68 mg Observations on 55 gouty subjects maintained on a low purine diet yielded an over all range of 190 to 999 mg of urinary urate per 24 hours with a mean of

now be considered to be incorrect since it seems likely that biosynthesis of urate does not require incorporation of precursors into pentose or desoxypentose nucleic acids In the metabolism of intermediate nucleotides phosphorus appears to be conserved by regeneration of pentose or desoxypentose phosphate and other phosphoric esters Classic bal

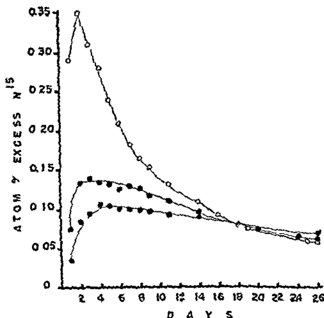


Fig 10A.—Rate of incorporation of N^{15} from ingested N^{15} labeled glycine into uric acid in 2 normal men (solid circles) and 1 gouty subject (open circles) who regularly excreted excessive amounts of urate in the urine Note marked increase of incorporation of N^{15} into the urate formed by the gouty subject for the first 10 days of the experiment (12)

ance methods therefore probably cannot be relied upon in such studies in gout isotope labeling being a more likely method

It is generally conceded that at least in the case of gout associated with polycythemia vera and other blood dyscrasias overproduction of urate resulting from increased turnover of nucleic acids plays a predominant role in the causation of gout However substantial evidence also points to urate overproduction in many cases of gout occurring under ordinary circumstances Excessive urinary excretion of urate on a low purine diet particularly in the face of distinct hyperuricemia

since the damage would obscure the main issue because of retention of all nonprotein nitrogen end products of metabolism including uric acid Such a change in emphasis seems justified if a specific renal defect in urate excretion were the primary cause of hyperuricemia in asymptomatic essential hyperuricemia and manifest gout it should be detectable even in the earliest stages of the disorder

These conclusions should not however obscure the high incidence of concomitant renal damage in gout and its importance as a complication in secondarily aggravating urate retention and the disabilities of the tophaceous form of the disease The high incidence of generally impaired renal function in gout amply confirmed by recent studies has never been adequately explained Pathologic examination of the gouty kidney tends to discount the role of urate deposits as such and of secondary pyelonephritis while emphasizing the frequency of nephrosclerosis Whether the incidence of vascular lesions is disproportionate to that expected in the age periods represented has not been made clear

Overproduction of Urate The chief objection to the urate overproduction theory has always been the frequency of urinary urate excretion levels within or below the normal range As already indicated many exceptions to this general trend show unequivocally augmented endogenous urinary urate excretion Moreover as already emphasized most gouty subjects with low normal or low levels of urinary urate excretion have one or another indication of kidney damage In these circumstances the quantity of urate excreted in the urine cannot be taken as a yardstick of the magnitude of urate production for appreciable amounts of urate may be excreted vicariously into the gastrointestinal tract (where urate is rapidly oxidized by the bacterial flora hence cannot be measured accurately) or deposited in the tissues or perhaps degraded in the tissues to some extent One would not for example attempt to gauge nucleoprotein metabolism in patients with renal insufficiency by the quantity of inorganic phosphate or nitrogen excreted in the urine

Another point made against the urate overproduction theory is that the urinary excretion of inorganic phosphate is said not to be increased to the extent expected with an accelerated nucleoprotein breakdown The available data on this point are too sparse and too unspecific to be evaluated The phosphate retention effect of concomitant renal damage must be taken into account in such studies Moreover the assumption that uric acid derives entirely from nucleoprotein degradation must

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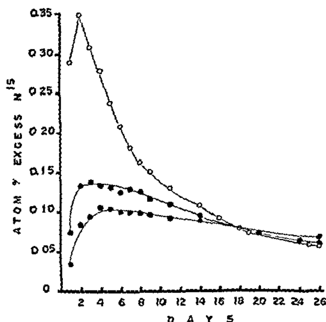


Fig 10A —Rate of incorporation of N from ingested N^{15} labeled glycine into uric acid in 2 normal men (solid circles) and 1 gouty subject (open circles) who regularly excreted excessive amounts of urate in the urine Note marked increase of incorporation of N^{15} into the urate formed by the gouty subject for the first 10 days of the experiment (12)

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and urate retention in the tissues (tophi), can hardly be otherwise interpreted (101 103) Direct support for overproduction of urate in such a case has recently been found (12) a gouty subject with intact kidneys and habitually excessive urinary elimination of urate was fed N^{15} labeled glycine a precursor of uric acid which contributes the nitrogen in position 7 of the purine ring For the first 3 days after in

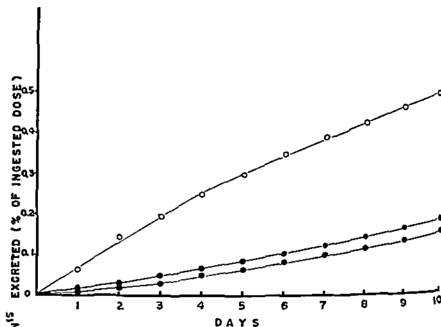


Fig 10B—Cumulative excretion of N as uric acid after ingestion of N labeled glycine in 2 normal males (solid circles) and 1 gouty subject (open circles) The gouty subject incorporated over 3 times the normal amount of N into uric acid (12)

gestion of the labeled glycine the N^{1} concentration of the excreted urate was approximately threefold that of normal subjects similarly treated thereafter it rapidly fell off and approached the normal levels (Fig 10A) At the end of 10 days the cumulative excretion of urate incorporated N^{1} in the gouty subject was approximately 0 5 per cent of the N^{1} fed a figure slightly more than 3 times the corresponding proportion in the normal controls (Fig 10B) These results make it quite clear that biosynthesis of urate from glycine in the gouty subject markedly exceeded the normal presumably with diversion of some glycine nitrogen from metabolic pathways ordinarily culminating in

urea formation to others leading to urate formation The rapidity with which large amounts of urate incorporated N^{15} appeared in the urine suggests that the major route of urate synthesis was not by way of nucleic acids which normally have a relatively slow turnover even in the case of PNA but that these were by passed through alternative more direct pathways presumably involving purine intermediates In a second gouty subject studied later similar results were obtained

How representative of gout these experiences may be remains to be determined It is wholly probable that varying degrees of this metabolic derangement obtain in different cases The distribution of points in Figure 9 would indeed suggest that in some cases even with out discernible impairment of renal function overproduction of urate if present at all is of such slight proportions as may not be readily demonstrable The cumulative effect over many years of even so slight an excess of urate formation may nevertheless eventually have clinical significance particularly if abetted by increasing difficulties in disposal of urate through the kidneys

The probability of urate overproduction in some cases of gout brings to the fore the problem of the site or sites of urate formation in man a point on which there is little information It is likely that there are important species differences which may make translation of animal experiments to man hazardous Thus in the bird the liver seems to be the principal organ for uric acid synthesis (30 145) This does not appear to be true in the dog It has been shown by Bollman and Mann (29) that uric acid formation in the hepatectomized dog continues at about the same rate as may be inferred to occur in the intact dog judging by the rate of allantoin excretion but oxidation of uric acid to allantoin is entirely prevented and uric acid is excreted in large amounts In man too there is indication of extrahepatic origin of at least part of the urate formed (47) Loffler and Koller (137) summarized the evidence in this connection for the predominant role of the bone marrow site of erythropoiesis and estimated that one third to one half of the normal total endogenous urate production derived from this source Presumably in gout associated with polycythemia vera and other blood dyscrasias with increased urate formation from accelerated turnover of DNA the bone marrow is the major site of excess urate synthesis Burian (46 47) however has directed attention to muscle as another important extrahepatic site of urate formation in man citing evidence for a transient rise in urinary urate excretion after exercise in support of this thesis Quick (154) was un

able to confirm this finding Nevertheless the recent indications of a by pass in urate synthesis involving formation of inosinic acid and related compounds (93) again raise the issue of muscle as a site of urate formation in normal and gouty subjects since hypoxanthine and adenine nucleotides and nucleosides are such important constituents of muscle metabolism As already pointed out, a relation of urate synthesis to muscle mass and metabolism might explain many hitherto obscure characteristics of gout

Acute Gouty Arthritis

Consideration of the causes of acute gouty arthritis is for the present a futile inquiry Of the multiplicity of mechanisms proposed in the literature in speculations on this point discussion here will be limited to those dealing with the role of uric acid *per se* the role of the "pituitary adrenal axis" and the role of allergy

Uric Acid per se The general concurrence of hyperuricemia with acute attacks in gout and the presence of urate deposits in and around the joints in chronic tophaceous gout has led to the prevailing impression that acute gouty arthritis is caused by uric acid itself To be sure acute gout may appear in patients with the gouty trait who show no distinct hyperuricemia at the time of the attack—the literature indicates that about 10 to 30 per cent of patients with gout *fail to have* definite hyperuricemia (36) However the incidence of such occurrences is steadily declining as methods for determining uric acid improve or they can now largely be explained by prior treatment with salicylates or other uricosuric agents

Uric acid causes acute gout it is alleged "when crystallization of the salt takes place in any tissue" whereupon "inflammation is suddenly lit up by its presence and a paroxysm of gout ensues" (86) To cite a more recent source (149) "The disease is marked by attacks in which the crystals of urate accumulate rapidly causing inflammatory reactions in and about joints With subsidence of the attack the deposits may be reabsorbed leaving no immediate residua

There is such a paucity of data concerning the morphology of acute gouty arthritis despite the countless times that acutely involved great toes have been incised *as a result of erroneous diagnosis* that histologic proof or disproof of this hypothesis is not available—if indeed histologic proof of the origin of acute gout is possible at all Occasionally acute gouty bursitis is encountered especially olecranon bursitis ap

parently precipitated by rapid filling of the bursa with urate deposits But on the whole there is little substantiation for the assumption that uric acid exerts any such violent vasomotor and inflammatory effects as characterize the sudden onset of acute gouty arthritis If uric acid has any pharmacologic action at all it is of a very low order at least in man As stated by A E Garrod (87) whose wide experience in inborn errors of metabolism gave him unusual insight into the mechanisms of gout "there is no conclusive evidence that uric acid and the urates as such exert any toxic influence upon the tissues and there is strong evidence that the pathological vice of sodium biurate like that of cystin is its tendency to be deposited in crystalline form in the tissues and especially in cartilage" Hench (110) also has expressed the opinion that uric acid has little or nothing to do with acute attacks and gives seven cogent reasons for this view

Examination of the literature reveals little basis for the widely held view that "uric acid salts injected intravenously have a very toxic action on the kidneys" (174) This impression appears to derive chiefly from experiments by Dunn and Polson (69) who injected enormous doses of uric acid (up to 1 0 Gm per kilogram) intravenously into rabbits and noted oliguria with increased blood urea nitrogen When the animals were killed this was explained by the necrosis of the distal segments of the renal tubules associated with precipitation of uric acid continued administration of smaller dosages produced "only minor results without cumulative effect" There are also the observations of Folin *et al* (75) who noted marked but transient edematous swelling of the kidneys in the dog associated with temporary uric acid storage and rise in plasma urea nitrogen after intravenous injection of substantial doses of uric acid (100 mg per kilogram) The claim (94 95) that diabetes may be produced by intraperitoneal injection of uric acid in rabbits with lowered blood glutathione induced by deficient diets has not been confirmed in the rabbit (58) or rat (97) Similarly an alleged alloxan like action of uric acid to which Conn *et al* (59 60) ascribe the glycosuria accompanying the increased urate excretion produced by ACTH is now generally discredited The basis for this hypothesis appears to have been a positive error in uric acid determinations caused by the presence of appreciable concentrations of glucose in the urine as pointed out by Bien and Troll (17)

In weighing the evidence for appreciable "toxic" action of uric acid the following points should be considered (*1*) The dosages of uric acid intravenously injected in animal experiments were relatively

large thus favoring precipitation in the collecting tubules How much of the ensuing damage was mechanical" and how much "toxic" it is difficult to judge (2) Lithium carbonate invariably was used to dissolve the uric acid and substantial amounts of lithium were therefore also injected It is now well recognized that lithium salts may cause damage to the distal convoluted and collecting tubules (155) as well as prominent neuromuscular and other effects (3) There are important species differences in the fate of injected uric acid in different animals and it is hazardous to translate findings in animals to assumptions in man the observations of Folin *et al* indicate this clearly In any event injection of uric acid into animals does not cause joint symptoms certainly nothing even remotely suggesting acute gouty arthritis

Acute gout cannot be produced in normal or gouty human subjects by uric acid fed by mouth injected intravenously or injected subcutaneously around the joints For example Berliner *et al* (15) studying nongouty males gave constant intravenous infusions of uric acid in doses up to 100 mg per kilogram with resulting elevations of serum urate to 26 mg per 100 cc the hyperuricemia persisting for several days No semblance of acute gout was produced In about half the subjects slight and transient nausea and vomiting developed 1 patient bed fast with advanced Paget s disease had a prolonged reaction marked by neurologic manifestations attributable to the large dose of lithium carbonate used as solvent and oliguria with temporary rise in blood urea nitrogen Folin *et al* (75) injected uric acid (about 20 mg per kilogram) intravenously into 9 gouty subjects without producing or aggravating gouty attacks in a single instance although a protracted further rise in serum urate to over 20 mg per 100 cc in 1 case was regularly produced Several patients showed transient retention of nonprotein nitrogen

Clinical experience also clearly indicates that hyperuricemia does not of itself provoke acute gouty arthritis If acute gout occurs at all in chronic nephritis with prolonged nitrogen retention and hyperuricemia it must be extremely rare In the blood dyscrasias in which there may be increased formation not only of uric acid but also of other purines acute gouty arthritis does occur but only in a small proportion of cases Even in persons with persistent and marked hyperuricemia due to the gouty trait acute gouty arthritis is the exception rather than the rule and is sporadic and unpredictable in occurrence There is no consistently significant change in the level of serum urate preceding during or following an untreated acute attack

of gout the urinary urate retention which may occur prior to an attack to be followed by a "urate flood" during and after the attack (137) as stressed in the older literature is not a regularly associated phenomenon Remission of acute gouty arthritis by colchicine is not accompanied by any significant change in serum urate level or urinary urate excretion If marked uricosuria and decline in serum urate concentration are produced by such agents as benemid or carinamide acute gouty attacks are not thereby prevented or abated in fact benemid like salyrgan may precipitate acute gout upon initiation of therapy In the case of ACTH cortisone salicylates and cinchophen all uricosuric agents that have abortive or analgesic effects in acute gout there is no correlation between the uricosuric effect and the degree of clinical response—marked uricosuria may be produced with little or no amelioration of symptoms

As to the provocative effect of urate deposition in the tissues there is every indication that precipitation of urate which appears to be a quite general phenomenon in chronic gout ordinarily is insidious Tophi in the ordinary course of events are wholly indolent in their inception and accretion even though they sometimes cause overt inflammation and pain acute gouty seizures do not occur for example in the external ear the most common site of visible tophus formation although secondary infection occasionally is encountered The almost invariable sequence of events in gout is that acute attacks come first and large tophaceous deposits if they appear at all follow years later It is the common experience that acute gouty arthritis is apt to involve joints that do not give roentgenographic evidence of large urate deposits (although some urate may well be present) and as more and more urate is thrown down in and around that joint the acute attacks are likely to migrate to other joints as yet relatively free of tophaceous involvement

All these objections should not obscure the fact that tophaceous deposits in the joints kidneys and elsewhere may and do act as foreign body irritants in chronic gout causing secondary inflammatory tissue responses predisposing to secondary infections and impinging upon neighboring structures There is no compelling reason however to accept the thesis that uric acid in itself is immediately responsible for the striking local and systemic disturbances in acute gouty arthritis the causes of which remain wholly obscure

There would seem to be more justification under the circumstances to turn suspicion upon presumptive precursors of uric acid in inter

mediary purine metabolism perhaps to consider also possible degradation products of uric acid Adenosine and its phosphorylated derivatives are known to have potent systemic and local effects when injected in small dosage (66–68 91 138 184 202) These effects include depressant action on the conduction system of the heart transient lowering of the blood pressure (largely due to peripheral vasodilation) a variable action on smooth muscle of the intestine and other organs contraction of the uterus relaxation of the bronchioles inhibition of water diuresis by the kidneys production of leukocytosis and local inflammatory reactions These actions of adenyl compounds are striking enough to suggest that they may play a role in the complex phenomena of inflammation following injury (67) ATP has also been indicted as a major factor in causing the manifestations of traumatic and ischemic shock (91 186) a theory with which Kalckar and Lowry (121) disagree The toxicity of these adenyl compounds precludes their use in the treatment of pellagra (178) and various other disorders in which they have been tried

Except in protracted large dosage adenine has very little effect (156 185) other than mild leukocytosis (157) among other things large amounts produce renal damage due to deposition of sparingly soluble 2 8 dioxypurine in the renal tubules ("adenine kidney" (9)) Guanine and hypoxanthine together with their respective nucleoside and nucleotide derivatives have little or no pharmacologic action Apparently therefore the effects of adenosine adenosine 5 phosphate adenosine-3 phosphate and adenosine diphosphate and triphosphate depend upon the presence of pentose and of the amino group in position 6 of the purine ring The relation of biologic activity to deamination and "ammoniogenesis" is however still obscure

Despite the variety of effects produced by adenyl compounds nothing suggesting acute arthritis has yet been described to occur with adenosine except by Thannhauser and Bommes (197) Our own efforts to induce an attack in intercritical gout by subcutaneous injection of 50 mg of adenosine over a susceptible joint have thus far ended in failure (220)

ALLERGIC STATE As pointed out by Linossier (132) Llewellyn (133) Gudzent (98) Lichtwitz (129) and many others certain aspects of the acute gouty attack resemble those of an allergic reaction The points of similarity include such features of acute gout as the periodic and paroxysmal nature of the attack with symptom free intervals provocation by small quantities of specific foods or alcoholic liquors in

certain predisposed subjects localization in joints as in the arthralgias of hypersensitive states onset with local circulatory disturbances notably circumscribed venous stasis manifested by swelling of adjacent veins livid discoloration of the skin and marked edema of the affected area and an allegedly high percentage among the gouty of skin hypersensitivity to various foods particularly grain meat and fish proteins (99) and to other agents (205) Just how much significance should be attached to these similarities which after all are not very distinctive or to the occasional concurrence of hay fever asthma migraine or urticaria in gouty subjects has not been made clear

Proponents of the allergic theory of gout for the most part concede that tissue hypersensitiveness alone would not explain the hyperuricemia urate deposits and other metabolic characteristics of the basic disorder It is in the evocation of the episodic acute attack and perhaps also of alleged abarticular manifestations of gout that the allergic state, superimposed upon the underlying derangement of metabolism is conceived to play its role this despite the fact that the characteristic onset in middle age the sex predisposition and the monoarticular predilection of the great toe are strange to allergy According to the allergic theory the hypersensitivity may be not only to nucleoproteins but to any food or to allergens in certain liquors or to bacterial products Indeed in conjectures going beyond the boundaries of true allergic mechanisms Gudzent (98) and Lichtwitz (129) postulated the liberation of histamine like substances from tissues after trauma operations physical exertion exposure to cold and emotional upsets—thus anticipating current speculations about the role of adenine derivatives and of stress and its effects on the pituitary and adrenal glands

The allergic theory has been interpreted quite literally by some who have translated the concept into practical terms of skin testing desensitization attempts and elimination diets The results of such efforts have never been made altogether clear Thus Gudzent (99) reported that in attempts to prevent acute gouty attacks by desensitization technics and elimination diets he had had "satisfactory" in part "surprisingly good" results in some patients but had failed in a smaller number no details or data are given The few other reports available on this subject are equally vague and difficult to evaluate When Hench in 1937 reviewed the general experience in this field he found the consensus to be that skin tests had little significance and elimination diets were of no particular value in the management of gout (109) The use of these measures is virtually abandoned at least in this country

Interest in this approach to gout has been revived in the last few years Harkavy (107) recently reported 3 cases in which acute arthritis interpreted as acute gouty arthritis was provoked by spontaneous or induced exposure to allergenic pollens or to the synergistic action of allergenic foods and pollens There can be little question that acute gouty arthritis may be precipitated in a gouty subject who happens also to be hypersensitive to one or another pollen or food by an allergic attack following exposure to the exciting agent In such instances probably more attention should be paid to the specific and non specific excitants of either exogenous or endogenous origin (107) which may provoke the typical allergic attacks in the usual shock organ (skin lung etc) and also acute gout in a susceptible joint What has not been established is whether this combination of events occurs often enough to play a significant role in the causation of acute gouty arthritis That chronic tophaceous gout also may be attributed to recurrent allergic attacks involving the joints thus causing irreversible inflammatory changes which favor the deposition of urates (107) is a speculation as yet without basis

The discovery of antihistaminic agents capable of preventing and arresting many expressions of the allergic response offers another method of assessing the role of allergy in acute gout Our own limited experience with pyribenzamine and similar drugs (220) indicates that they are generally ineffective in the treatment of acute gouty arthritis and this appears to be the experience of others so far as can be ascertained Ferrannini and Pergola (73) however report some success with antihistamines Whether the striking effect of adrenocorticotropic hormone in acute gout bears any relation to its action in bronchial asthma and other allergic states cannot as yet be stated

Role of Pituitary and Adrenal Glands Whatever the immediate agency of acute gouty arthritis the problem remains how such diverse precipitating causes as local trauma dietary and alcoholic overindulgence infections surgical procedures and emotional upsets operate to incite an acute attack Robinson *et al* (159) and Hellman (108) drawing upon Selye s concepts have made the interesting suggestion that these several causes of acute gout activate a common mechanism that they are in effect nonspecific stresses which elicit an alarm reaction and this takes the form of an acute attack in the individual predisposed to gout (166) Attractive as this idea may be at first glance it is based primarily on observations (108 159) in only 3 cases suggesting that acute gouty arthritis is precipitated in the transitory stage of depressed

adrenocortical activity which is presumed to occur 3 or 4 days after abrupt withdrawal of ACTH administered to patients with intercritical gout In our hands (104) an acute attack developed only once in 8 attempts of this kind It is true as many investigators have noted that when ACTH therapy is terminated, an exacerbation of acute gouty arthritis may occur a day or two after remission This phenomenon is attributable however to inadequate or insufficiently prolonged administration of ACTH probably representing reappearance of the underlying disorder when the suppressive action of ACTH is prematurely withdrawn as occurs in rheumatoid arthritis and many other diseases

A Nonspecific stresses ——→ Stimulate hypothalamo-hypophyseal response ←—— Epinephrine

Trauma
Infection
Operation
Dietary excesses
Emotional upset

Stimulate hypothalamo-hypophyseal response
↓
Increased anterior pituitary secretion
↓
Increased adrenal cortical secretion
↓
Eventual corticoid lack
↓
Alarm reaction (acute gout)

B ACTH therapy
↓
Increased adrenal cortical secretion ——→ Corticoid lack
↓
Relief of acute gout

Cessation of ACTH therap
↓
Corticoid lack
↓
Precipitation of acute gout

The diagrams above represent these concepts of the mechanism of stress as an inciting agent in acute gout (*A*) and of the allegedly paradoxic effects of ACTH therapy (*B*) in terminating attacks of acute gouty arthritis (amply confirmed) and also in provoking acute attacks (as yet insufficiently corroborated) Wolfson *et al* (215) expressed this hypothesis as follows

A characteristic endocrine disturbance in the patient with clinical gout is

his failure to restore promptly a normal adrenal cortical status when a state of lack of adrenal glycocorticoids ("corticoid lack") is induced by the withdrawal of exogenous ACTH by a decrease in the rate of secretion of endogenous ACTH or by an increase in the rate at which the peripheral tissues are utilizing adrenal glycocorticoids Normally this corticoid lack is counteracted by activation of the hypothalamo hypophysis which stimulates the anterior pituitary and thus the adrenal cortex but in gout this mechanism is absent or sluggish apparently because of a defective hypothalamo-hypophyseal response In some gout patients there is more severe impairment of the hypothalamo hypophyseal mechanism and chronic hyposecretion of ACTH with resultant impairment of ability of the adrenal cortex to respond normally hence the need for unusually large doses of ACTH for optimal therapeutic results in acute gouty arthritis

In addition Wolfson and Cohn (214) postulate secretion of an abnormal adrenocortical androgen in gout based on the finding of extremely low urinary excretion of 17 ketosteroids in 11 gouty subjects (212) and an imbalance in elaboration of various 11 oxysteroids Wolfson *et al* (215) conclude that "by the conjoint operation of these two endocrine disturbances in some as yet unknown manner acute gouty arthritis appears to be an endocrine disorder produced by the occurrence of an abnormally persistent state of corticoid lack in an individual who is predisposed by a particular type of hereditary endocrine disturbance to develop the particular symptomatology of gout

Despite the attractiveness of the general concept of stress in gout (166) and the ingenuity of the argument for endocrine factors in the causation of acute gout the evidence for a key role of the pituitary and adrenal glands is not convincing although the possibility that these important glands may participate in some way has by no means been excluded It can no longer be assumed that because ACTH exerts beneficial effects in any one disease that that disease necessarily is the expression of dysfunction of the pituitary or adrenal glands It seems apparent now that the principal action of ACTH is through some peripheral tissue response common to a wide variety of diseases this seems to be borne out in gout by the prompt amelioration of acute gouty arthritis by injection into the joint of Compound F (113) Certain it is that gout does not occur spontaneously in any of the disorders of the pituitary or adrenal glands associated with either hypofunction or hyperfunction of these glands Moreover colchicine in dosages which have such a striking therapeutic effect in acute gout does not stimulate either gland significantly otherwise this drug presumably would be effective also in rheumatoid arthritis and other diseases which respond favorably to ACTH

The basis for assuming an abnormal adrenocortical androgen in gout also is insecure Hollander *et al* (114) did note decreased 17 ketosteroid excretion in some cases of gout but Tarnopolsky *et al* (194) found urinary 17 ketosteroid levels within the normal range in 7 of 8 gouty patients studied In measurements of urinary 17 ketosteroid excretion in 10 of our own patients with gout * the following values were obtained 4 9 7 5 7 8 8 0 8 1 9 1 10 3 11 2 11 5 and 14 2 mg per 24 hours These levels tend to be on the low side of the normal range found by the method employed (9 to 14 mg per 24 hours) but only one value in a 69 year old patient was far below the normal minimum

In summary from the preponderance of available evidence gout appears indeed to be as A E Garrod (87) surmised an inborn error of metabolism based upon an alternative and slightly divergent path of metabolism As a result of this derangement a disproportionate quantity of simple nitrogen and carbon precursors of uric acid is diverted from the main metabolic channels culminating in urea and carbon dioxide formation to pathways leading to urate formation In some cases of gout this divergence of metabolism presumably incorporates increased formation and breakdown of nucleic acids In the ordinary circumstances of "essential hyperuricemia and overt gout however, it is more likely that nucleic acid formation is largely by passed through the enhanced synthesis of simpler purine intermediates

Chronic tophaceous gout results when the rate of urate formation exceeds the capacity to dispose of urate In such circumstance there is no recourse but deposition of urate in the tissues a process which is facilitated by the difficult solubility of urates It follows that this process is accelerated by more severe degrees of the metabolic derangement leading to urate overproduction and by high dietary intake of urate precursors if renal and other excretory routes are unable to cope with the extra load Deposition of urate may be slowed or obviated even in the face of markedly increased urate production by increased excretion of urate particularly through the kidneys possibly also in minor degree by degradation of urate in the body The kidneys therefore play a key although ordinarily a secondary role in determining the rate of urate deposition in the tissues This role does not seem to depend upon a constitutional intrinsic inferiority in respect to renal excretion of urate for which no acceptable evidence has been found but rather upon a high incidence of secondary renal damage as yet not

* We are greatly indebted to Dr Louis J Soffer for these data

altogether satisfactorily explained As renal damage progresses a vicious cycle is instituted by which more urate is retained and further impairment of excretory function ensues

Acute gouty arthritis does not appear to be attributable to urate itself Possibly precursors or degradation products of uric acid may be the immediate cause of symptoms but no direct evidence for this is at hand The role of the pituitary and adrenal cortex in eliciting acute attacks is wholly conjectural as is that of the allergic state At present one can only speculate upon the special mechanisms which apparently operate sporadically within the framework of the over all metabolic anomaly to provoke the manifestations of acute gouty arthritis

MANAGEMENT OF GOUT

While the theoretic considerations outlined in the foregoing discussion have brought about a distinct change in the philosophy of the management of gout no cure has been forthcoming and treatment remains largely a matter of trial and error in the empiric use of drugs of whose mechanisms of action little or nothing is known Despite these limitations however substantial progress has been made in recent years in the prophylaxis and control of acute gouty attacks in the prevention of tophaceous disabilities and even in reduction of size of established tophi

There is no one universally applicable scheme for the management of gout Current principles of prophylaxis and therapy can be set forth but these must be adapted to individual requirements and patiently accommodated to changing needs by constant regulation of drugs and diet according to the clinical and laboratory findings in the individual case

The general aims of management depend upon the presenting phase of the disorder The discussion which follows will therefore be divided into a consideration of the several problems presented by asymptomatic essential hyperuricemia acute gouty arthritis intercritical gout and chronic tophaceous gout

Asymptomatic Essential Hyperuricemia It is doubtful that any active measures are indicated in persons with essential hyperuricemia who have never had an acute gouty attack since manifestations of gout may well never occur and if they do often not until late in life Restriction of purines from the diet may be prudent and high fat or alcohol intake is unwise

Acute Gouty Arthritis Palliative treatment of acute gouty arthritis includes bed rest in the more severe attacks positioning of the affected joint to minimize discomfort liberal use of analgesics such as salicylates and sedatives to combat pain and stiffness and a trial of local application of warm or cold compresses Fluids should be forced and a soft bland diet prescribed

For specific therapy colchicine is still the drug of choice Treatment should be started as soon as possible to obtain the most effective results If begun at the first intimation of an impending attack the onset of which is often heralded by twinges of pain tenderness or stiffness in a joint or other indisposition recognized by the observant patient the episode may be aborted by ingestion of 0.5 mg of colchicine every hour or two until a total of 3 or 4 mg has been taken If treatment is not started until the attack is full blown colchicine is given in doses of 1 mg every 3 hours until the attack subsides or until diarrhea, nausea or vomiting ensue To continue the drug beyond the development of severe gastrointestinal upset is not only distressing to the patient but dangerous because of the toxic properties of colchicine however looseness of the bowels due to anxiety and irritability may occur very early in treatment and should not be confused with colchicine toxicity Ordinarily substantial relief of pain and inflammatory manifestations is obtained after a total dosage of 6 to 8 mg The effective total dosage for any one patient tends to be fairly constant in successive attacks so that a record of amounts given should be kept for future reference Diarrhea is apt to persist for several days after colchicine is discontinued but may be controlled with paregoric Occasionally intravenous administration dramatically relieves severe attacks of acute gout particularly if given early Since the preparations commercially available for injection also contain large amounts of iodide and salicylate it should first be ascertained whether there is any sensitivity to these agents

While the acute symptoms usually subside within a few days some tenderness and swelling of the affected joint is apt to persist for longer periods if the attack has been severe or prolonged To avoid recurrence and the possibility of involvement of other joints unnecessary exertion and food and alcohol indulgence should be avoided and if indicated small preventive doses of colchicine (usually 1 mg daily) should be resumed for a while as soon as tolerated

Nothing is known concerning the mechanism of action of colchicine in acute gouty arthritis a highly specific effect of the drug It may be

presumed from the minute effective dosage that the action is upon some enzyme system since the order of magnitude involved virtually excludes any other possibility If so the enzyme system in question remains to be identified Current conjecture favors some relation to purine metabolism and to the striking action of colchicine on mitotic division a process involving desoxypentose nucleic acids

ACTH is an effective agent in the treatment of acute gouty arthritis (62 104 108 139 159 160 179 199 211 214 215) and offers distinct advantages over colchicine in some cases Indeed as experience with ACTH grows and its potentialities are more fully exploited it may displace colchicine as the preferred form of initial treatment in severe acute gouty attacks To abort incipient attacks 2 or 3 intramuscular injections of 25 mg 6 hours apart often suffice *In severe cases* of established acute gouty arthritis particularly in those responding unsatisfactorily to colchicine ACTH therapy should be initiated with 1 or 2 injections of 50 mg a total of 100 to 150 mg daily being given in divided doses the first day or two An occasional patient (3 of 26 in our experience) will require more than 150 mg ACTH a day for control of symptoms The dosage is then slowly tapered off to 75 50 and finally to 20 or 25 mg a day for 4 or 5 days the treatment schedule and duration depending upon response Symptoms often reappear if the suppressive effect of ACTH is terminated too soon in the manner observed in many other disorders—a phenomenon interpreted by some however as provocation of a new attack by corticoid lack As further insurance against such recurrence it is advisable to give 1 or 2 mg of colchicine daily concurrently with ACTH (211 215) and to continue this dosage of colchicine for several weeks after subsidence of the acute symptoms

Wolfson *et al* (215 216) have found that long acting ACTH in repository form offers a further simplification of treatment of acute gout terminating 12 of 13 attacks with a single injection of 100 mg This form of ACTH therapy warrants additional exploration as does intravenously administered ACTH

Severe attacks that do not yield satisfactorily to full doses of colchicine usually respond well to ACTH if given in sufficient amount and *conversely* undue persistence of symptoms after ordinary doses of ACTH is likely to cease upon full treatment with colchicine Appropriate adjustment of ACTH and colchicine therapy therefore is almost always rewarding in accelerating relief of even the most refractory acute gouty arthritis and thus represents a significant advance in management The usual precautions with ACTH therapy even for such

short periods should of course be observed Congestive failure due to sodium and water retention is a hazard in the older age group represented and may require cessation of ACTH treatment and institution of mercurial diuresis (104) hypertension is a not uncommon accompaniment of gout and requires some attention sleeplessness following ACTH injections due to excitation may occur an occasional patient has an allergic reaction to the drug or vehicle

The mode of action of ACTH in ameliorating acute gout like its suppressive effects in numerous other disorders is still unexplained As shown by Thorn *et al* (198) and confirmed by many other investigators ACTH increases urinary uric acid excretion if given in sufficient dosage (104) It has been suggested that this increased urinary output may indicate augmentation of urate production by ACTH (76) but the accompanying reduction in serum urate levels (104) argues against this Moreover Setten *et al* (11) using intravenously injected N^{15} labeled urate in man as a measure of urate turnover rate found no indication of accelerated isotope dilution i e no evidence of increased urate formation after administration of ACTH The renal function studies of Ingbar *et al* (116) in man and of Friedman and Byers (82) in the rat indicate clearly that the uricosuric action of ACTH is attributable wholly or in large part to suppression of tubular reabsorption of urate

In any event no correlation can be made out between the degree of uricosuric effect and the clinical response in acute gout since urinary elimination of urate may be greatly increased by ACTH and the serum urate significantly lowered with little or no amelioration of the acute attack Whatever the mechanism of the antiphlogistic action of ACTH in acute gout therefore its effects cannot be ascribed to increase in urinary urate excretion or fall in serum urate levels

In the experience of most observers cortisone in doses of 100 to 300 mg per day has proved disappointing in the treatment of acute gouty arthritis the response being less consistent and more delayed than with ACTH (28 62 125 215 220) however some have noted good results (78) The reasons for this generally inferior action of cortisone in apparently equivalent dosage are not clear It may be significant that as Hollander (113) has pointed out compound F (hydrocortisone) affords rapid relief when injected into the affected bursa or joint in acute gout, whereas cortisone does not

Cinchophen once as highly regarded in the treatment of acute gouty arthritis as colchicine (204) has no place in the modern man

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Wolfson *et al* (215 216) have found that long acting ACTH in repository form offers a further simplification of treatment of acute gout terminating 12 of 13 attacks with a single injection of 100 mg *This form of ACTH therapy warrants additional exploration as does* intravenously administered ACTH

Severe attacks that do not yield satisfactorily to full doses of colchicine usually respond well to ACTH if given in sufficient amount and conversely undue persistence of symptoms after ordinary doses of ACTH is likely to cease upon full treatment with colchicine Appropriate adjustment of ACTH and colchicine therapy therefore is almost *always rewarding in accelerating* relief of even the most refractory acute gouty arthritis and thus represents a significant advance in management The usual precautions with ACTH therapy even for such

holic beverages as specific incitors of acute gouty arthritis notably rum heavy wines Bordeaux red wines and champagnes It is the general practice and our own to interdict all alcoholic liquors when there is frequent recurrence of acute gout despite the meager evidence in support of such arbitrary management Some of the most experienced observers of gout convinced of the futility of such measures permit limited or even free consumption of alcohol Certainly there are innumerable gouty subjects who can imbibe liberally without apparent harm

The history of gout is replete with examples of acute gouty arthritis precipitated by overindulgence in food What is not so clear is which articles of food should be held accountable and how far one should go in restricting the diet for the purpose of minimizing acute attacks in intercritical gout There is general agreement that purine rich foods should be shunned In regard to protein restriction opinion is divided Limitation of meat fish and fowl consumption was and perhaps still is the general rule but how rigidly these foods should be restricted cannot now be stated Most gouty subjects seem to tolerate dietaries providing daily meat rations without apparent ill effects but some particularly those in the late stages of chronic tophaceous gout appear to suffer diffuse pain and stiffness and even overt acute attacks after large meat meals As to fat intake there is good evidence that a high fat diet may provoke acute gout (134 143) hence restriction of fat for this purpose as well as for weight control seems clearly indicated

The general trend in dietary management of intercritical gout therefore is to prescribe an adequate well rounded diet which however is low in purines poor in fat and sometimes more or less limited in regard to the meat fish and fowl permitted Support for restrictions of this kind comes from experience in countries suffering protracted food shortages for example Brugsch (40) noted a marked decline in acute attacks among the gouty in Germany at the conclusion of World War I and the same is true currently in England

Our own policy in regard to dietary regulation in intercritical gout is motivated by the consideration that the problem of recurrent acute attacks should not obscure that of tissue urate deposition in chronic gout and by the recent knowledge concerning the lively biosynthesis of urate from simple nitrogen precursors such as ammonia and glycine particularly in the gouty subject A rather rigorous dietary program by present day standards consequently is advised In cases of long standing gout with frequent recurrence of acute gouty arthritis the initial diet given is low in purines poor in fat and restricted in protein

agement of the acute attack While it is undoubtedly a potent analgesic and antiphlogistic the availability of more effective and less hazardous medications makes its use unwarranted Neocinchophen despite its analgesic properties is of little help and benemid we find to be of no value in the treatment of acute gouty arthritis (220)

Intercritical Gout For centuries attempts have been made by all manner of means to prevent recurrence of acute gouty attacks notably by a variety of dietary restrictions and by protracted administration of various drugs That none of these prophylactic regimens has proved convincingly successful is evidenced by the prevailing multiplicity of recommendations some as dogmatic as they are conflicting

So long as the mechanisms of acute gouty arthritis remain unknown prophylaxis must remain an empiric effort But there is an intrinsic difficulty in evaluating even such empiric preventive programs the marked innate variation in susceptibility to attacks of different patients Some patients flout all regulation with impunity for years others are refractory to even the most rigid attempts at control This has encouraged a defeatist attitude in some quarters On the other hand there is a general tendency to credit infrequency of attacks to one or another therapeutic program without due regard for the unpredictably long intervals between attacks that may occur spontaneously this has led to overenthusiastic acceptance by some of even the most unlikely regimens The truth probably lies between these two extremes a decent respect for dietary regulation and judicious use of prophylactic medication adjusted to individual patient requirements may well have value in lessening the frequency and severity of acute attacks To establish this however would require long term carefully conducted and recorded observations in a large series of patients with data suitable for objective statistical analysis No such study has yet appeared

Dietary regulation in the intercritical periods of chronic gout actually has two distinct objectives (*1*) prevention of recurrent acute gouty attacks (*2*) retardation of development of the deformities and disabilities of chronic tophaceous gout However in the past these usually have not been clearly separated Only the former will be discussed here the effects of dietary restriction on uric acid formation and excretion are more appropriately discussed under the management of chronic tophaceous gout

Intolerance to specific foods which regularly provoke acute gouty attacks is an occasional occurrence in our experience and an obvious indication for proscription More common is recognition of alco

tinued low purine diet He found this program "highly successful" noting only 3 recurrences of acute gout in 37 patients treated for periods of 6 months to over 5 years Talbott (190) also prescribes colchicine in symptom free periods to gouty patients who regularly suffer one or more acute attacks each year finding the effects less specific than in control of the acute attack but nevertheless beneficial--no precise data are given The dosage is varied from one or two tablets every week in patients who have but one attack a year to a regular daily ration of one or two tablets throughout the year in cases with very frequent recurrences Talbott has noted no evidences of toxicity after prolonged periods on this dosage nor has there been any indication of acquired tolerance to the drug Prophylactic colchicine has been employed sporadically by others for the most part with only indifferent success (personal communications)

Our own practice with patients subject to recurrent attacks of acute gout and those with diffuse joint pains associated with chronic tophaceous gout is to advise regular prophylactic use of colchicine in conjunction with the dietary restrictions already described together with administration of uricosuric agents usually benemid when indicated The dosage of colchicine is carefully adjusted by trial and error to individual requirements Ordinarily 1 or 0 5 mg every night sometimes on alternate nights will suffice in more severe cases 1 5 mg nightly may be required--dosage levels which over an observation period of many years have been well tolerated by most patients have thus far caused no evident bone marrow depression or liver damage and appear not to evoke drug tolerance Altogether 35 patients have been maintained on this regimen for periods varying from 6 months to over 10 years with regular follow up in most instances In many cases final judgment is as yet impossible because of the infrequency of attacks prior to treatment and the short period of observation Of this series 4 patients previously subject to very frequent severe and prolonged attacks each year have obtained only partial relief 1 is still having about 9 attacks each year another had two major and two minor episodes in the past year and the third and fourth still suffer two or three severe attacks each year In the remaining 31 acute attacks have either been virtually absent or limited to occasional minor episodes readily aborted by increased dosage of colchicine In 9 cases this prophylactic program appears to have made the difference between virtual incapacitation because of frequent interruption of work and restoration to partial or complete activity Omission of colchicine for any length of time

(50 to 70 Gm per day) consisting for the most part of cereals grain products eggs cheese milk nonleguminous vegetables and fruits The diet is combined with prophylactic drug therapy and after prolonged regulation is usually liberalized somewhat by addition of small portions of meats fish or fowl each week At present we have no satisfactory objective data to justify this onerous dietary restriction It is our impression that such a diet helps to minimize the frequency and severity of acute gouty attacks in many patients subject to persistent relapses but that dietary limitations alone no matter how rigorous will not forestall acute paroxysms in most cases For example we have observed acute gout to occur in patients maintained under hospital ward control on the Kempner rice fruit regimen the ultimate in low purine protein fat and sodium intake Such ancient dietary devices as milk strawberry citron or cherry diets have long since dropped out of fashion although a cherry diet recently has been reintroduced (20)

It is interesting in this connection to note Garrod s (86) comment on an exclusively vegetable diet which was advised by certain physicians in his day and was claimed to keep some patients free of inflammatory symptoms and even to lead to disappearance of chalk stones (tophi) While Garrod advised limitation of meat intake to that which is necessary for the proper sustenance of the body he found that gout could not be successfully treated by complete abstinence from meat alone It has since been well established that acute gout may occur in vegetarians However the widely cited statement of Das Gupta (63) that gout is a common disorder among the vegetarian sects of Nepal (incidence 60 to 70 per thousand population with 40 per cent among females and children commonly involved!) appears to have been based upon an error in diagnosis He may have been referring to the "burning feet" syndrome a nutritional deficiency disease now known to be widespread in some parts of India

In respect to the prophylactic use of drugs to prevent recurrence of acute seizures in intercritical gout there is increasing evidence that colchicine and perhaps certain uricosuric agents may be helpful in this regard particularly if employed in conjunction with dietary restriction It is quite extraordinary that colchicine known for centuries to be an effective agent in the treatment of established attacks has not been more extensively investigated as a prophylactic agent in prevention of acute gout Some 15 years ago Cohen (56 57) suggested its intermittent use for this purpose in interval gout advising ingestion of 0 5 mg three times daily for one week in every four in conjunction with a con

between good clinical response and lowering of serum urate levels was by no means consistent. In regard to the hepatotoxicity of cinchophen, Bartels had not encountered serious difficulties at the time his report was made (1943) Occurrence of hepatotoxic reactions in some of his patients since then has led Bartels to abandon the use of cinchophen altogether (personal communication) While cinchophen is still employed for this purpose by Hench (111) and others, it is now generally held that, with other effective and less toxic agents for prophylaxis of acute gouty arthritis available the risk attending use of cinchophen though small is rarely justified

Bauer and Klemperer (8) have found protracted administration of salicylates to be of no value in preventing attacks of acute gout. This has been our experience too although the drug in ordinary dosage is a useful analgesic particularly in controlling diffuse joint pains in chronic tophaceous gout. Prolonged use of ACTH as a prophylactic in view of its undesirable side reactions high cost, and great inconvenience involved, would seem to be neither feasible nor desirable (104) Cortisone in continuous daily dosage of 25 to 100 mg is now being tested as a prophylactic agent (personal communications) It appears to be useful in abating chronic joint pains and stiffness in tophaceous gout, but thus far has proved to be of doubtful value in preventing recurrence of acute gouty arthritis and has many of the disadvantages of ACTH With regard to prolonged use of benemid, it is not yet possible to judge the effects of the sustained uricosuria and lowered serum urate levels produced by this agent on the incidence of acute gouty attacks Preliminary experience (193 220) fails to disclose any benefit from the use of benemid for this purpose It has no apparent analgesic or antiphlogistic action and, indeed tends to precipitate acute attacks within the first week of administration

As general measures which have proved useful in the management of intercritical gout mention should be made of regular exercise reduction of weight in overweight subjects and avoidance of undue trauma, particularly to the feet.

CHRONIC TOPHACEOUS GOUT It has already been pointed out that, from all indications selective deposition of urate in tissues occurs more frequently in chronic gout than is *apparent from the development of* visible tophi indeed it may be looked upon as a more or less regular consequence of the disorder in its late stages While resultant overt disability is the exception rather than the rule nevertheless this general trend should be taken into account in the management of a gouty pa

tient especially if there is evidence of some degree of renal impairment

Since urate presumably is deposited in the tissues when the rate of urate formation exceeds the rate of its elimination the problem of controlling the rate of urate deposition would appear to be open to two methods of attack (1) Attempts to minimize urate formation by dietary restrictions and (2) attempts to increase urinary urate excretion by the use of uricosuric agents

Although both of these measures have been extensively employed in the management of gout for many years little factual information is available concerning their efficacy in the prevention of disabling tophaceous gout For one thing their use hitherto has been oriented almost exclusively toward obviating acute gouty attacks largely on the assumption that uric acid itself is immediately responsible for the precipitation of acute gouty arthritis little attention appears to have been paid to possible effects on tophus formation in chronic gout For another the uricosuric agents hitherto employed chiefly cinchophen and salicylates proved to be too toxic for continuous administration in the required dosage and so had generally been given in accordance with one or another scheme of interrupted dosage thus permitting re accumulation of urate deposits in the body Finally it is as difficult to evaluate the efficacy of measures designed to deter the development of urate deposits in chronic tophaceous gout as it is those intended to minimize acute gouty attacks The occurrence of visible tophi at best an uncertain gauge of the extent of urate deposition is erratic and unpredictable in the ordinary course of events Measurement of the pool of readily miscible urate by means of N^{1} labeled uric acid is not possible on a large scale and the content of tophi moreover is not readily miscible with the injected urate Estimation of the total excess urate excreted in the urine by protracted administration of uricosuric agents a crude approximation of the total mobilizable urate store has been carried out as yet in relatively few cases Prolonged study of urinary urate excretion under controlled conditions of dietary intake is required to accomplish this

Convincing direct evidence that omission from the diet of one or another dietary component will obviate the development of tophi or decrease the miscible pool of urate is not at hand However considerable data are available concerning the nitrogen and carbon precursors of uric acid and the effects of various foods on urinary urate excretion and serum urate levels The cumulative effects of such dietary components should be taken into account in the management of chronic

gout even though direct evidence of their influence on the course of the disease is still wanting

That ingestion of preformed purines in purine rich foods markedly increases urinary urate excretion (as much as 100 per cent if taken in large amounts) and may cause significant elevation of the serum urate has been confirmed many times since it was first clearly shown by Burian and Schur (48) Meats fish and fowl if taken in sufficient quantity or meat extracts also cause an appreciable rise in urate production for the most part due to their content of preformed nucleotides Nitrogen sources which are free of preformed purines however also contribute significantly to urate formation as shown by classic metabolic balance methods by Folin (74) Mendel and Brown (144) and many others this has been fully substantiated by more recent isotope studies indicating the utilization of ammonia and glycine nitrogen in the biosynthesis of urate in man (5 12 167) Diets high in fat but low in carbohydrate and protein cause a sharp decline in urinary urate excretion with concomitant rise in serum urate (2 134) such changes are also effected by the equivalent fat catabolism in the fasting state (127) High carbohydrate diets cause little or no measurable increase in urinary urate excretion in ordinary balance experiments although isotope studies reveal utilization of carbon from carbohydrate sources for urate synthesis

It would therefore seem entirely justifiable to omit preformed purines from the diet and to limit the intake of protein and fat in establishing a regimen intended to minimize urate formation and thus slow down the rate of tophus formation in chronic gout To be sure since urate is synthesized from simple nitrogen and carbon precursors derived from all forms of dietary protein fat and carbohydrate it is impossible to exercise complete control over endogenous urate formation by dietary restriction Indeed it is likely that dietary regulation may be least efficacious in the very patients in whom retardation of urate formation is most to be desired—in those with abnormally high rates of urate biosynthesis Nevertheless it seems altogether reasonable not to add to the metabolic burden of the gouty subject by furnishing unnecessary sources of preformed purines and nitrogenous purine precursors in the diet

In considering the importance of dietary regulation in chronic tophaceous gout one should appreciate that renal efficiency plays a key role in clearing urate from the plasma If the extra urate formed as a result of dietary excesses can be excreted in its entirety none is re

tained in the tissues Some of our patients for example show no rise in serum urate levels and presumably deposit little or no urate in the tissues after a large meal since the extra urate formed is promptly excreted in the urine In many others however the serum urate rises appreciably even if the urinary excretion of urate is somewhat in creased—the kidneys apparently cannot handle all of the extra load and such urate as cannot be excreted presumably is largely deposited in the tissues It is to the steady accumulation of such increments over the years that the development of the deformities and disabilities of chronic tophaceous gout may be ascribed

Since dietary restrictions can exercise only partial control of urate formation it is rational to supplement dietary regulation with adminis tration of uricosuric agents to minimize urate deposition in the tissues By thus limiting urate formation and simultaneously increasing urinary urate excretion a maximal negative urate balance can be achieved in time this prevents formation of new tophi in the patient with chronic tophaceous gout and may lead to mobilization of tophi already formed

Many substances are known to increase the urate clearance and urinary excretion of urate cinchophen salicylates ACTH and corti sone carinamide benemid salyrgan diodrast and other agents (174) Of these only cinchophen (2 phenylquinoline 4 carboxylic acid) sali cylates ACTH and cortisone carinamide (4 carboxyphenylmethane sulfonanilide) and benemid (p (di n propylsulfamyl) benzoic acid) are of practical therapeutic interest

Cinchophen also known as atophan has recently been extensively reviewed by Hueper (115) Its uricosuric properties were first de scribed in 1908 by Nicolaier and Dohrn (148) who studied its effects on normal human subjects Shortly thereafter Weintraud (204) used the drug in the treatment of gout he noted that whereas the uricosuric ef fect of cinchophen could be elicited for only a day or two in non gouty subjects prolonged uricosuria occurred in a case of gout This observa tion was confirmed by Zuelzer (221) who proposed this continued uri cosuric response as a test for gout Weintraud further showed that the increased urinary excretion of urate following cinchophen administra tion was not accompanied by augmented excretion of total nitrogen or phosphorus indicating that the uricosuric effect was not due to acceler ation of urate production from nucleoproteins but rather to mobiliza tion of urate deposits in the tissues and body fluids He recommended protracted administration of cinchophen in doses of 2 to 3 Gm daily together with a low purine diet It is interesting to note that Wein

traud envisioned the possibility of reducing the size of tophi by continued use of cinchophen He gave the drug regularly for several weeks to a patient with chronic tophaceous gout and thought that the urate deposits became smaller the inflammatory reaction less intense and the discharge from fistulating tophi more abundant and more fluid

Cinchophen was thereafter widely employed in the management of chronic gout chief emphasis being placed upon its capacity to reduce the serum urate level and to exercise an analgesic and antiphlogistic effect in chronic and acute gouty arthritis There is no convincing evidence in the literature on cinchophen that prevention of tophus formation or mobilization of established tophi ever was definitely accomplished by protracted administration of the drug the only explicit references to this subject mention failures (52 171) This is not surprising for in view of its toxicity cinchophen was of necessity almost universally given in intermittent dosage Since urate rapidly reaccumulates in the body when the drug is discontinued intermittent administration presumably results in little net loss of urate from the tissues In any event the hepatotoxicity of cinchophen has discouraged further extensive trial of the drug as a practical form of protracted uricosuric treatment in chronic tophaceous gout We have not employed it at all except for special studies Neocinchophen which appears to be somewhat less hepatotoxic has only feeble uricosuric properties (220)

Salicylate in the form of willow bark was employed in the treatment of podagra by Dioscorides in the first century (96) It still has a place in the management of gout chiefly by virtue of its analgesic and antiphlogistic properties As a uricosuric agent salicylate is effective only in high dosage (7 72 96 103 118 124 220) causing a significant increase in urinary urate excretion and decrease in blood level ordinarily only when 4 to 5 Gm or more are given daily The uricosuric effect is usually markedly enhanced by concomitant administration of alkali

There is considerable variation from patient to patient both in the degree of uricosuric response to the same dosage of salicylate and in the potentiating effect of sodium bicarbonate which itself does not increase urinary urate elimination (Fig 11) When 3 Gm of aspirin or sodium salicylate is given the effect on urine and serum levels is usually minimal with smaller doses renal retention of urate with a greater or lesser rise in serum urate is the rule Because of the individual variation in uricosuric response to salicylate however it is important to control dosage levels in protracted administration of the drug by

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tent administration as in the case of cinchophen Jennings (118) recommended 4 to 5 Gm daily for 3 successive days in the week Since the uricosuric effect of salicylate terminates soon after discontinuance and is often followed by a day or two of urate retention there is little or no net loss of urate from the body tissues in patients following such a regimen of interrupted dosage This fact doubtless contributes to the absence in the literature of any clear indication that prevention of tophus formation or mobilization of established tophi has been accomplished by use of salicylates Benedict *et al* (11) did find a marked decrease in the miscible pool of urate in a patient with chronic tophaceous gout who had taken 2 6 to 4 0 Gm of aspirin daily for 3 months but even in this instance no change in size or consistency of the patient s tophi was observed

In our own studies we have been able to maintain salicylate administration for many months in uninterrupted daily dosage of 5 Gm for the most part as enteric coated sodium salicylate in 3 patients who tolerated the drug reasonably well 2 of the patients presented the most advanced and disabling stage of chronic tophaceous gout with frequent appearance of fresh tophi Once the combined dietary restriction salicylate regimen was established no new tophi appeared After some 6 to 9 months unequivocal disappearance of long present large tophi was noted The mobilization of urate was marked in the 2 advanced cases in which 90 to 100 Gm of excess urate was removed from the tissues over this period Details are given elsewhere (218)

No data are available with regard to the protracted use of ACTH and cortisone as uricosuric agents in chronic tophaceous gout In view of their side effects and high cost it is doubtful that these agents will prove practicable for this purpose

Carinamide (21 22) and benemid (16 23 27 50 203) were originally developed by Sharp and Dohme as agents for sustaining high blood levels of penicillin and para aminosalicylic acid by interference with renal excretion of these antibiotics Wolfson *et al* (210) noted that carinamide also increases urinary uric acid excretion in normal human subjects a finding which directed our attention to trial of this substance as a uricosuric agent in gout (101 103 104 219) A mean increase of 60 per cent was found in the urinary urate excretion of 13 gouty subjects given a daily dosage of 12 Gm carinamide on 8 Gm daily dosage the mean increase in urinary urate excretion was approximately 40 per cent A marked and sustained decline in serum urate level was produced by carinamide in these dosage levels Administra

determining the urate in the urine and serum Such estimations require special precautions including the use of uricase (158 217) because of the presence of salicylate oxidation or conjugation products which give color with the common uric acid reagents The most troublesome of these metabolites is gentisic acid (217) which should first be extracted from the urine or serum to avoid significant errors even with uricase (217)

Despite much earlier controversy over the mechanism of action of

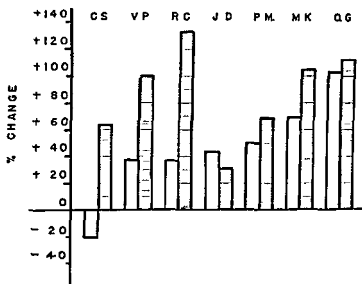


Fig 11 —Uricosuric effect of salicylate 5 Gm daily dosage (hollow bars) and potentiating effect of concomitant administration of sodium bicarbonate 5 Gm daily dosage (shaded bars) Note marked variation in response of 7 different gouty subjects

the uricosuric effect of salicylate (96) recent evidence of Friedman and Byers (79 80) indicates clearly that salicylate in appropriate dosage causes marked inhibition of tubular reabsorption of urate and this presumably accounts for most of the increase in urinary urate excretion

The large dosage of salicylate required to produce marked uricosuria is a serious handicap to its practical use in sustained uricosuric therapy of chronic tophaceous gout Mental confusion tinnitus and deafness gastrointestinal complaints hyperventilation and other toxic manifestations of salicylism usually appear often after relatively short treatment in the older age group in question This has suggested intermit

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tion of the drug could be maintained uninterruptedly day after day for months in many gouty patients However the large number of tablets to be consumed daily was objectionable and although the drug is of low toxicity (22) gastrointestinal symptoms drug rash and drug fever developed in a sufficient number of patients to cause some concern (103)

Benemid became available to us in 1950 It soon became apparent that this was an exceedingly potent uricosuric agent of low toxicity the most promising for protracted use in chronic tophaceous gout that we

TABLE I

Effect of Benemid on Urinary Uric Acid Excretion of Gouty Subjects on Low Purine Restricted Protein Diet (105)

Benemid Gm /Day	Patients No	Urinary Uric Acid 1st Day		
		Range Mg / 24 Hr	Mean Mg /24 Hr	Mean % Inc
2 0	12	477–1 877	1 102	+119 0
1 0	16	508–1 870	959	+ 88 8
0 5	11	606–1,545	921	+ 82 5

Benemid Gm /Day	Urinary Uric Acid 1st Week				Urinary Uric Acid 2nd Week			
	Patients No	Range Mg /24 Hr	Mean Mg /24 H	Mean % Incr	Patients No	Range Mg / 24 H	Mean Mg / 24 H	Mean % Inc
2 0	14	453–1 258	852	+67 0	7	551–1 011	761	+35 7
1 0	15	362–1 363	756	+52 2	7	361–1 120	754	+22 2
0 5	10	462–1 065	711	+46 6	8	381– 796	556	+23 5

had yet tested Our initial experience (101) was with 2 Gm in divided daily doses in 14 gouty subjects this produced a mean increase of 58 5 per cent in urinary urate excretion associated with a sustained fall in serum urate to approximately half the initial level Smaller doses of 1 Gm daily were also found to be effective (101) so much so that doses in excess of this amount are not now employed in many cases Our more recent experience with benemid as a uricosuric agent in chronic gout (105) is summarized in Table I It will be noted that in dosages as low as 0 5 Gm daily a mean increase of 46 6 per cent in urinary urate excretion was observed for the first week and 23 5 per cent in the second week of drug administration The rapid and striking lowering of the serum urate level obtained is illustrated in Figure 12 On 2 Gm benemid daily the mean reduction in serum urate level of 18 gouty subjects was 42 per cent in the first week and 47 per cent in the second week on 1 Gm daily it was 33 per cent in the first week

and 34 per cent in the second week (24 cases) on 0 5 Gm daily it was 27 per cent in the first week and 28 per cent in the second week (20 cases) In most instances these lowered serum urate levels which can be reduced to the upper limit of normal or often well below if desired can be sustained for many months by continued benemid administration Upon discontinuance of medication the serum urate rises to or toward the initial hyperuricemic level within a few days

In view of this experience we now begin benemid administration

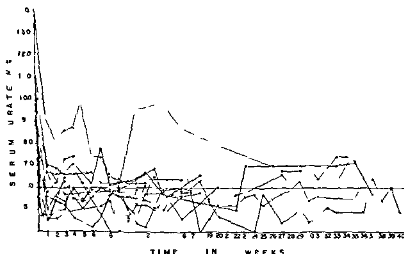


Fig 12 —Effect of benemid (1 Gm daily) on serum urate levels in 14 cases of chronic gout maintained on the drug 10 weeks or longer The line at 6 mg % represents the approximate upper limit of normal for serum urate (105)

in 1 Gm or 0 5 Gm daily dosage depending upon clinical circumstances after obtaining a baseline of urinary urate excretion and serum urate concentration with the patient on a low purine restricted protein diet (Fig 13) Dosage is slowly adjusted according to the laboratory and clinical response usually to 0 5 Gm daily although 1 Gm daily or more occasionally may be advisable When there is a satisfactory uricosuric response and sustained fall in serum urate to desired levels it is often practicable to liberalize the dietary protein intake somewhat perhaps with an associated increase in benemid dosage to maintain the lowered serum urate level Proper regulation requires individualization of treatment according to the personal requirements of each patient and all adjustments in diet and drugs should be guided by urine

and serum urate determinations as well as by clinical considerations

The intensity and duration of the uricosuric effect of benemid like that of all other uricosuric agents varies significantly in different subjects given the same drug dosage and maintained on the same low purine low protein diet For example normal individuals excrete distinctly increased urinary urate for only the first day or two even

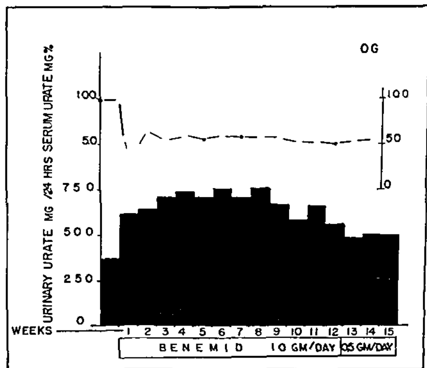


Fig 13 —Patient O G with chronic gout showing sustained uricosuric effect of benemid over a 15 week period (105) The patient was maintained throughout on a constant low purine restricted protein diet

though administration of benemid is continued in dosage of 1 or 2 Gm daily A total of only approximately 1 Gm of excess "endogenous urate can thus be removed from normal man if the diet is kept constant In gout of several years duration some 3 to 10 Gm of excess urate in all can usually be mobilized by continued use of benemid or other uricosuric agents whereupon the daily urinary urate excretion returns to control levels despite continued administration of the drug It is only in chronic gout particularly in chronic tophaceous gout that

the deposits of urate in the tissues are so extensive that many weeks or months of daily intensive uricosuric therapy are required to deplete the tissue reserves in one such case we have mobilized over 100 Gm of excess urate from the tissues without apparent diminution in the uricosuric effect (218) At present we continue uninterrupted uricosuric therapy in such patients until the urinary excretion of urate re

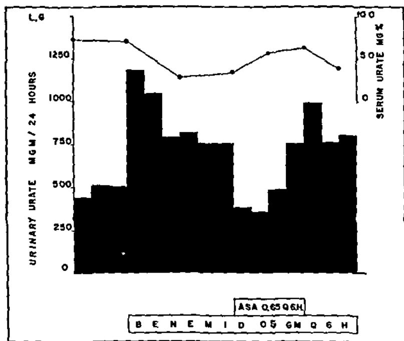


Fig. 14 —Suppressive effect of addition of aspirin (2 6 Gm daily) to benemid (2 Gm daily) on urinary urate excretion in a patient with chronic gout maintained on a low purine restricted protein diet (10)

turns to control levels when dosage is reduced or interrupted for a respite of several weeks or months depending on circumstances

Sirota *et al* (169) made simultaneous renal clearance studies of inulin p aminohippurate urate sodium potassium chloride and phosphate in 10 gouty subjects They found a consistent and striking increase in urate clearance usually beginning within 40 minutes of oral administration of 2 Gm of benemid and persisting for 24 hours There was no significant change in GFR so that the ratio of urate clearance

and serum urate determinations as well as by clinical considerations

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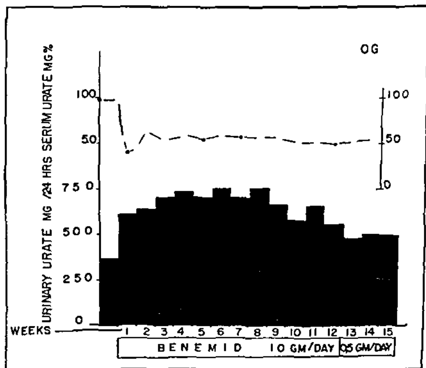


Fig 13—Patient O G with chronic gout showing sustained uricosuric effect of benemid over a 15 week period (105) The patient was maintained throughout on a constant low purine restricted protein diet

though administration of benemid is continued in dosage of 1 or 2 Gm daily A total of only approximately 1 Gm of excess "endogenous" urate can thus be removed from normal man if the diet is kept constant In gout of several years duration some 3 to 10 Gm of excess urate in all can usually be mobilized by continued use of benemid or other uricosuric agents whereupon the daily urinary urate excretion returns to control levels despite continued administration of the drug It is only in chronic gout particularly in chronic tophaceous gout that

distinct bone marrow depression have not been encountered No in dications of renal or hepatic damage have appeared Obviously in sufficient time has elapsed to make any definitive judgment of possible late toxic effects of benemid and its administration still requires unre mitting vigilance for early detection of undesirable side reactions

From the experience with benemid it would appear that there is now available a practical uricosuric agent of great potency which can be administered orally in uninterrupted daily dosage for indefinite periods and with little apparent risk of significant toxicity Such a drug may make it feasible to extend greatly the objectives of management in chronic tophaceous gout Hitherto these objectives have been limited to palliation and when necessary surgical excision or amputation of troublesome tophaceous deposits The present aims of management are distinctly more ambitious It is proposed by combined dietary restriction and appropriate medication taken regularly under proper control to prevent the development of deforming and disabling topha ceous deposits in chronic gout and even to mobilize tophi already formed Modest success in these directions already has been achieved (105 218) Thus no new tophi have appeared in any of our patients with chronic tophaceous gout once the combined diet-benemid regi men was fully established even in those who had had regular crops of superficial urate deposits at short intervals before therapy was ini tiated moreover discontinuance of benemid was followed by resump tion of overt new tophus formation within weeks or months Reduction in size and even disappearance of established tophi particularly in the feet has become a more and more unequivocal achievement of pro tracted benemid therapy (218) The results would seem to augur well for the future management of patients with chronic tophaceous gout provided both patient and physician are prepared to exercise the in finite patience and perseverance required for optimal results

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to inulin clearance rose strikingly the average peak being more than four fold the control value A slight to moderate decline in clearance of PAH was also noted All other renal functions tested were not significantly affected by benemid

Benemid therefore is a potent and apparently highly selective uricosuric agent in normal and gouty man inhibiting the inexplicably high tubular reabsorption of urate from the glomerular filtrate Although itself filtered through the glomeruli benemid would appear to act exclusively upon tubular transport mechanisms suppressing tubular secretion of PAH diodrast penicillin PAS and PSP and the tubular reabsorption of urate The precise mechanism and site of these benemid effects are not known Of interest is the finding (105) that the

TABLE II
INCIDENCE OF SIDE REACTIONS TO BENEMID IN VARIOUS DOSAGES (105)

	2 GM /DAY	1 GM /DAY	0 5 GM /DAY
Total no of patients	18	24	20
Instances of reactions	11	9	5
Nausea anorexia constipation	2	4	4
Drug rash	1	1	0
Renal colic	2	0	0
Acute gouty attacks	6	4	1
Bone marrow depression	0	0	0

uricosuric action of benemid is suppressed by concomitant administration of salicylate (Fig 14) itself a uricosuric agent but not by ACTH

Side reactions to benemid (Table II) thus far have rarely been disturbing enough to require discontinuance of the drug (105 193) The most common complaint in our experience is gastrointestinal upset usually mild and controlled by sodium bicarbonate and liberal fluid intake In 1 of our patients a drug rash developed 2 patients who had previously suffered repeated attacks of renal colic due to urate calculi complained of pain in the flank after starting benemid in 2 Gm daily dosage This experience emphasizes a hazard in the use of benemid and other potent uricosuric agents in such instances it is important to use smaller doses to force fluids and to give alkalinizing salts to keep the urinary urate in solution An interesting complication of benemid therapy is its propensity to provoke acute gouty attacks in the first few days of administration despite increased urinary excretion of urate and lowering of the plasma urate level Patients should be prepared for this possibility and instructed to take covering doses of colchicine upon the first intimation of an acute attack Evidences of

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Clinical Aspects of Ganglionic and Adrenergic Blocking Agents

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SURGICAL interference with the sympathetic nervous system has been attempted on man for 62 years but only within the last 20 years has its sphere of usefulness been properly defined. Because sympathectomy is apparently efficacious in a wide variety of disease states the search for drugs which would mimic its results has been assiduously going on. Certain compounds have now been found that will produce some of the effects of sympathectomy.

A brief summary of the present concept of the functional activity of the autonomic nervous system will help to understand the type of activity these drugs can modify. The autonomic nervous system is one of the protective mechanisms which coordinates body activity to meet changing environmental conditions. To do this a complex relationship must exist between the various elements of the central nervous system and the chemical and endocrine balance of the body (72) (Fig. 1). In the last analysis the autonomic nervous system acts on effector cells in all body organs by stimuli coming through ganglionic synapses from higher centers. The ganglions of the parasympathetic system are generally in close proximity to the effector cells while the ganglions of the sympathetic portion may be quite far removed and connected to effector cells by nonmedullated nerve trunks. The preganglionic sympathetic fibers synapse widely with many ganglionic cells and thus give the effect of a mass discharge in contrast to the discrete and limited

distribution of the postganglionic parasympathetic fibers For normal transmission in a ganglion acetylcholine must be released by the preganglionic nerve terminal and when so released must be able to stimulate the postganglionic neuron

The two divisions of the autonomic nervous system are chemically similar in the mechanism of transmission of impulses across ganglions but differ distinctly in the stimulation of the effector cells by postganglionic neurons In the parasympathetic system and in certain por

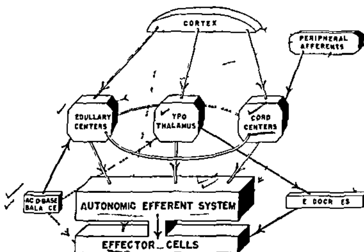


Fig 1 —Interrelations of the autonomic nervous system

tions of the sympathetic system acetylcholine is elaborated at the effector cell and serves to stimulate it whereas the majority of postganglionic fibers of the sympathetic nervous system elaborate an epinephrine like substance at the effector cell for stimulating the cell Dale (28) has divided the autonomic nervous system into the adrenergic and cholinergic systems Drugs modifying the major effects of sympathetic nervous system stimulation do so either by their action on the adrenergic effector cells or by interference with the transmission of impulses through ganglions or centrally by preventing the elaboration of sympathetic impulses Many compounds have several sites of action so that their specific pharmacologic effects cannot be easily delineated

Direct depression as well as reflex inhibition of centers which govern vascular tone can be accomplished by a number of drugs of apparently unrelated structure This pharmacologic approach particularly

to the problem of hypertension most nearly approximates the ideal solution Unfortunately so little is known about the nature of the chemical configuration necessary for such activity that an orderly and systematic program of synthesis and development is not yet possible Current research in the field is concerned with the exploitation and application of drugs which by the process of eliminating more peripheral sites of action have been judged to act centrally Such drugs as veratrum viride dihydro ergot alkaloids and 1 hydrazinophthalazine apparently cause significant peripheral dilatation by interfering with central vasoconstrictive mechanisms Obviously any central depressant may also modify the actions of the autonomic nervous system and decrease the number of sympathetic impulses transmitted to effector cells.

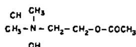
However only those drugs will be considered here which either act by interfering with the transmission of impulses in the ganglions or by modifying the manifestations of effector cell response. Interference with transmission of impulses through certain portions of the sympathetic nervous system can be obtained by means of spinal anesthesia or locally by injections of procaine in the region of the sympathetic ganglions But these will not be discussed here

GANGLIONIC BLOCKING AGENTS

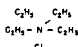
One way of interfering with transmission of sympathetic impulses is to prevent the action of acetylcholine on the ganglion cells (78) This can be accomplished by drugs which in themselves are inactive but which compete with acetylcholine at the ganglion cell This type of block by competition can be produced by a number of drugs of the quaternary amine variety with chemical structures similar in some respects to that of acetylcholine (Fig 2) Tetraethylammonium (TEA) (1–3) hexamethonium (93) pentamethonium (93) and to a lesser degree banthine (58) will produce some degree of ganglionic block

Recently a diquaternary ammonium dibromide N N N N 3-penta methyl N N diethyl-3 aza pentane 1 5 diamonium-dibromide (Ciba 9295) has been demonstrated to have some ganglionic blocking ability in human subjects but at present it does not seem to be as effective as the methonium compounds (9a 71a) Curare too blocks transmission of impulses across autonomic ganglions but it also blocks impulses at the neuromuscular end plate which produces muscular as well as autonomic paralysis

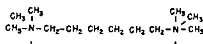
A ganglionic block by drugs causes a diminution in all the sympathetic and parasympathetic autonomic functions so that the body is *not able to respond to usual environmental changes* The effects produced by an autonomic block in man may best be described by the reaction to an intravenous injection of TEA (73) (*1*) Partial ptosis of eyelids (*2*) partial dilatation of pupils (*3*) loss of accommodation (*4*) congestion of nasal mucous membranes (*5*) reduction of salivation (*6*) tachycardia (*7*) cutaneous vasodilatation with obliteration



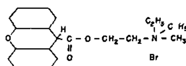
Acetylcholine



Tetraethylammonium chloride



Hexamethonium
Hexamethylene bistrimethyl ammonium diiodide



Banthine
Beta diethyl aminoethyl xanthene 9 carboxylate methobromide

FIG 2 —Chemical structure of various ganglionic blocking agents

of temperature gradient (*8*) anhidrosis (*9*) arteriolar and venous dilatation (*10*) orthostatic hypotension (*11*) a fall in blood pressure in those patients with inelastic arterial systems or hypertension (*12*) cessation of propulsive gastrointestinal motility (*13*) loss of bladder tone and (*14*) loss of temperature regulating mechanism Peripheral resistance is decreased and blood flow in the extremities and kidneys is increased along with an increase in cardiac output when the patient is supine In the presence of pulmonary hypertension pulmonary pressure and pulmonary capillary resistance are decreased (41 45 53)

The duration of the blockade after a single injection of TEA will

vary considerably depending upon the environmental factors For example the temperature gradient is more easily obliterated in a room at 80 F than in one at 65 F and the change in skin temperature will persist for a longer time in a relatively warm environment Further more the response of normal subjects under the same conditions varies considerably with the individual The disappearance of the manifesta tions of blockade too varies to some extent with each subject and this reflects to some degree the intensities of tone in certain portions of the autonomic nervous system

Whether different blocking agents will produce different degrees of block on different organ systems is not clearly understood at present Paton (92) believes that hexamethonium is not equally active on all autonomic ganglions and that the spectrum of ganglionic sensitivity seems to vary with each ganglionic blocking agent He believes that tetramethonium has more and pentamethonium less effect than hexamethonium on the intestine as compared to their effects on the superior cervical ganglion Such differences though they might be demonstrated in the animal are relatively insignificant in comparison to the variable effects of total blockade in man

However when the drugs are administered intravenously there are apparently significant differences between TEA and hexamethonium or pentamethonium Tetraethylammonium causes a transient tingling or chilly feeling which gradually passes through the body this is absent with the methonium compounds Tetraethylammonium produces a metallic taste the methonium compounds do not The dose of TEA needed to produce a relatively complete blockade is approximately 7 to 9 mg per kilogram however certain effects may be noted with as little as 1 5 mg per kilogram The intravenous doses of the methonium compounds vary from 0 4 to 1 5 mg per kilogram approximately one tenth that of TEA And finally the effect of the methonium compounds lasts considerably longer Arnold and Rosenheim (7) who compared the effects of the two drugs in hypertension believe that paralysis of accommodation and bowel and bladder disturbances were less promi nent with pentamethonium iodide than with TEA although they gave no evidence to support this belief

Tetraethylammonium is quite irritating when injected subcuta neously On the other hand 53 hypertensive patients who were given subcutaneous injections of pentamethonium and hexamethonium for several months apparently suffered no difficulty (105) Oral adminis tration of either compound is not particularly effective the drugs being

poorly absorbed although some blocking activity can be achieved with oral doses of hexamethonium in excess of 1 Gm

In our opinion there is no decided qualitative difference in the blocking action of TEA and the methonium compounds Their ability to compete with acetylcholine in producing ganglionic blockade seems to be beyond doubt Theoretically methonium compounds appear somewhat better than TEA being five to ten times as active per milligram dose and apparently having a somewhat longer activity (18) Evidence indicates that the methonium compounds produce a more complete blockade of the peripheral circulation than TEA (100) The methonium salts have until recently been prepared only as the bromide and the iodide and therefore had the disadvantage that they may predispose to bromism or iodism when given in large doses over a period of time The chloride salt has now been made available

Clinical Use of Ganglionic Blocking Agents

Though ganglionic blocking agents have been tried in a wide variety of diseases their practical usefulness is limited for the following reasons (*1*) they have a transient action even in the case of the methonium compounds (*2*) they produce a sufficiently complete blockade of the autonomic nervous system so that these effects particularly orthostatic hypotension are always serious problems (*3*) they do not achieve as complete a blockade as paravertebral block spinal anesthesia or sympathectomy

In Hypertension With the widespread use of sympathectomy for hypertension it was anticipated that ganglionic blocking agents might help to control hypertension and also to evaluate the possible response of the hypertensive patient to sympathectomy (64 73) Tetraethylammonium produced minimal changes in blood pressure in young normotensive individuals in the supine position On the other hand almost all hypertensive patients under the same conditions showed a prompt and profound fall in blood pressure which then gradually returned to its previous level within minutes to hours Although the blood pressure had returned to its control level orthostatic hypotension and other evidences of autonomic blockade often persisted (Fig 3) It was anticipated that the extent of the fall in blood pressure and the duration of the lowered pressure following administration of these compounds might be a suitable criterion for selecting patients with a greater degree of neurogenic vasoconstrictor tone However these

drugs produced profound falls in blood pressure in almost all elderly persons with inelastic arterial systems regardless of the initial height of pressure patients with nephritis coarctation of the aorta, or toxemia of pregnancy also had essentially similar decreases in blood pressure

A number of clinical reports indicate that TEA may be useful in determining vasoconstrictor tone (60 95 114) An almost equal number of reports show that this procedure is of no avail in predicting the

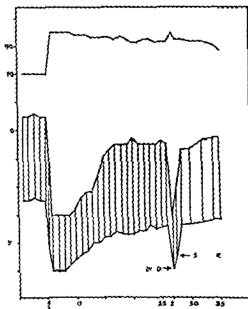


Fig 3 —Effect of 0 2 Gm tetraethylammonium intravenously on hypertensive patients Upper curve heart rate lower curve arterial pressure Abscissa indicates time in minutes arrow at 5 minutes indicates time of administration of the drug

response to sympathectomy (14 62 110) After several years experience with TEA we believe that this type of drug is useless in differentiating between neurogenic and other types of hypertension

The rise in blood pressure in any individual depends mainly on three factors (*1*) elasticity of the arterial system (*2*) amount of blood being ejected into the arterial system and (*3*) rate of outflow from the arteries With the sudden vasodilatation of the arterioles produced by a generalized autonomic blockade the rate of outflow from the arterial system will promptly increase with a resultant drop in blood

pressure A more profound drop in blood pressure will occur in patients with relatively inelastic arterial systems than in those with relatively elastic arterial systems Furthermore arterial systems under high pressure with concomitant loss of elasticity will have a greater fall in pressure than those under low pressure with an equal change in the rate of outflow (64) This explains the large changes in pressure in hypertension and the lack of change in the normotensive subject It also may explain why elderly individuals have a more profound fall in pressure despite relatively low initial levels than young people The diminished blood pressure under these circumstances will prevail until the cardiac output has increased sufficiently to replace in the arterial system the blood that was suddenly removed by arteriolar dilatation When this occurs the blood pressure gradually returns to control levels even though there is continued evidence of some degree of peripheral vasodilatation With the production of autonomic blockade there is a concomitant increase in heart rate to 20 to 30 beats per minute This may be sufficient to alter the diastolic pressure and thus fail to reflect the cardiovascular situation found after sympathectomy

Another factor influencing the extent of the fall in blood pressure is the change in blood and extracellular fluid volume in both normal and hypertensive individuals (64 112) In subjects who have undergone hyperhydration by the administration of large amounts of salt and water TEA or hexamethonium causes relatively little change in blood pressure or even a slight elevation in pressure After dehydration with low blood volume there is a severe fall in arterial pressure following ganglionic blockade—to the point of syncope—suggesting again that the diminished volume of blood returning to the heart and thus to the arteries may influence the change in pressure This significant difference in response with hyperhydration and dehydration may be due to the change in venomotor tone permitting the pooling of some of the blood volume in the venules (32) Thus a greater proportion of the circulating volume is lost with a low blood volume than with a high one It is also likely that neurogenic vasomotor tone may be diminished with a larger blood volume while with dehydration it may be somewhat increased The depressor response noted in patients therefore depends to some extent on the state of hydration rather than on inherent neurogenic vasoconstrictor tone These are the reasons why the compounds under discussion are ineffective agents for selecting patients with excessive neurogenic vasoconstrictor tone

The short duration of action of TEA along with the fact that it must be administered intravenously or intramuscularly precludes its

efficacy in the management of hypertension The autonomic blockade, with its attendant immobility of the gastrointestinal tract reduction of salivation mydriasis and bladder paralysis produced by the drug makes a patient quite uncomfortable with its continued use In an occasional patient the fall in blood pressure following injection of the drug has resulted in an immediate and lasting disappearance of hyper tensive headache (64 73) In a few patients who experienced recent severe elevations in arterial pressure a single injection of the drug de creased the pressure to previous hypertensive levels In some patients with hypertension and dyspnea from heart failure the drug not only lowered the pressure but diminished the degree of dyspnea

Though these minor effects may be of help in some cases they do not seem to be sufficiently great to warrant recommending the general use of TEA for hypertension or its complications

Many enthusiastic accounts of the use of methonium compounds for hypertension have appeared recently in the British literature (19 43 96 99 105 115) They are similar to our earlier experiences with TEA No large series of patients has been studied Perhaps the most enthusiastic report is that of Smirk and Alstad (105) who reviewed the effects of pentamethonium and hexamethonium in 53 patients treated for 2 to 14 months by subcutaneous administration of these compounds The daily dose ranged from 15 to 225 mg and was large enough to produce some degree of orthostatic hypotension but not so profound as to prevent the patient from maintaining the upright posi tion Repeated administration led to some degree of tolerance which could be acquired within a few days The dosage needed to produce a given effect would sometimes continue to increase for weeks Hypo tensive symptoms developed in some patients but tended to disappear in the course of regular administration of the drug The drug seemed to be particularly helpful in relieving the many complications of hyper tension Of 29 consecutive cases with severe headaches 27 had sub stantially complete relief and 7 patients with spontaneous attacks of dizziness were completely relieved Papilledema disappeared after 2 months or more of treatment Patients with heart failure and breath lessness exhibited appreciable improvement Of special interest were 4 patients with hypertension and renal insufficiency in whom lowering of the arterial pressure was not associated with a rise in nonprotein nitrogen or other evidence of impaired renal function Smirk and Alstad believe that the subcutaneous administration of methonium compounds is a practical method of managing hypertension In some of their patients besides tolerance bromism also developed

Lockett *et al* (69) studied the effect of the methonium compounds in 34 hypertensive patients After a 2 week control period of bed rest the drug was administered for 2 weeks the patients continuing at bed rest Nearly all of the patients exhibited a fall in pressure with the initial period of bed rest and there was a further slight fall with the intramuscular administration of the methonium compounds But when the patients were put on large oral doses of the drug and allowed to become ambulatory pressure rose to the initial levels despite doses as large as 4 Gm a day Other workers who have used the drug orally have not found it to be efficacious for long term treatment

Freis *et al* (43a) studied 32 hypertensive patients who received hexamethonium by subcutaneous injection as suggested by Smirk Six of 14 with malignant hypertension have had a remission of the malignant phase and 4 others have had similar remissions with the addition of 1 hydrazinophthalazine Of 16 patients with sustained hypertension 6 had sustained reductions in blood pressure and 4 more enjoyed reductions after the addition of 1 hydrazinophthalazine Oral administration of hexamethonium up to 1 0 Gm appeared to be less effective and more unpredictable

The most enthusiastic report of the control of hypertension by oral drug therapy was given by Schroeder (100a) With the combined oral administration of hexamethonium in gradually increasing doses to as much as 500 mg every 4 hours and 1 hydrazinophthalazine in increasing doses to 100 mg every 4 hours he was able to lower the blood pressure markedly and temporarily maintain the lower levels in every case There was considerable variation in individual requirements of both drugs He noted no instances of tolerance to either drug in fact certain patients required less hexamethonium after a month or two of normal blood pressure Of 60 patients on this regime 30 have had sustained normotensive levels Of 22 patients with malignant hypertension 8 are normotensive and 12 slightly hypertensive

In Peripheral Vascular Disease The multiple clinical manifestations of peripheral vascular disease render correct evaluation of the efficacy of any drug or procedure extremely difficult There are at present some 80 different drugs for which some efficacy is claimed Quite obviously none is specific

It has been proposed that production of a generalized arteriolar dilatation in the presence of vascular insufficiency would shunt blood away from the involved area in favor of the normal vascular beds and that as a result there would be a still greater ischemia in the

involved extremity (30) With the production of a generalized autonomic blockade and the attendant fall in blood pressure blood flow in the involved extremity may be greatly impaired at the time the arterial pressure is lower than its usual level This will produce more symptoms of ischemia which disappear with the return of the arterial pressure However thereafter blood flow is increased in the involved extremity as well as in other areas along with an increase in the cardiac output Thus in individuals who do not have severe grades of obliterative arterial disease but have a considerable component of increased vasoconstrictor tone in the extremities the production of a generalized blockade is followed by an increase in blood flow in the extremities It is unlikely however that generalized autonomic blocking agents will produce greater increases in blood flow than will local paravertebral block or spinal anesthesia with metycaine or procaine In general TEA increases the blood flow 7 to 8 times measured by means of the venous occlusion plethysmograph as compared to a fifteen fold increase in blood flow following paravertebral lumbar block in normal subjects (9) A recent study using hexamethonium in doses of 50 to 100 mg intravenously indicates however that there is a greater degree of sympathetic inhibition with this compound than with TEA as judged by the rise in blood flow and that it approaches but does not achieve complete blockade (100) Another study on changes in skin temperature in normal subjects and in patients with peripheral vascular disease showed that both pentamethonium and hexamethonium produced a greater increase in skin temperature more constantly than did TEA (18) It was noted that in 18 of 31 tests there was no significant increase in skin temperature or blood flow in the upper extremities though there had been consistent changes in the lower extremities

These drugs will be most effective when there is a high degree of neurogenic vasoconstrictor tone and least effective in the presence of obliterating arteritis In some instances injections of either type of compound may have dramatic results and symptoms may be relieved for much longer than might be expected after the other manifestations of autonomic blockade have disappeared Exactly why pain is relieved under these circumstances remains obscure Presumably a vasoconstrictor reflex cycle abolished as a result of ganglionic blockade does not again develop

A single injection of a drug such as TEA will in a remarkable number of instances relieve the pain in acute thrombophlebitis of either

the deep or the superficial variety Fisher (37) reported that in 26 of 52 patients a single injection relieved the pain apparently through producing some degree of venodilatation The relief of pain and the development of warmth in the extremities varied from only a few hours to permanent relief

Blocking agents have been found useful in treating painful vasospastic lower extremities in which the pain apparently arose from venospasm without evidence of thrombophlebitis The ankle edema of some of these patients may also be relieved In an occasional patient with arteriosclerosis obliterans and evidence of ischemia of the lower extremities a single injection of TEA has immediately so relieved the pain that the disability did not recur for several weeks (13 23 73)

While autonomic blocking drugs will produce some relief of the vasospasm associated with Raynaud s syndrome the need for frequent injections especially if TEA is used precludes their effective use (13 23 36) In patients with the shoulder arm syndrome these drugs will relieve pain and the associated vasospasm Hexamethonium has similar action except that the concomitant vasodilatation will last longer

On the whole however drugs that will produce paralysis of the sympathetics resulting in vasodilatation for only a short time cannot be effectively used for patients with long standing peripheral vascular disease and should not displace sympathectomy in the management of these cases The drugs may be of some value as a diagnostic tool in evaluating the degree of sympathetic vasoconstrictor tone which might be obliterated by sympathectomy However complete vasodilatation may not be achieved and the failure of a patient to exhibit satisfactory dilatation should not rule out the possibility that sympathectomy might be of benefit Surgical sympathectomy is still a procedure of choice in the management of chronic vasoconstrictive ischemic states in the lower extremity

In Causalgias and Other Painful States That procaine infiltration of local ganglions will block certain types of pain has been known for some time Such relief can be achieved in some patients with herpes zoster and in patients with posttraumatic painful states generally termed causalgia It appears that TEA and the methonium compounds may also relieve this type of pain (13 21 23 24 36 102) This is perhaps the most important use for these drugs In some instances in which sympathectomy failed to relieve the pain injections of TEA have achieved complete eradication of the painful state It is also useful in the differential diagnosis of the pain syndrome of a conversion neurosis and that of a true causalgia

Generally repeated injections are required for the relief of pain of the causalgic state though in occasional instances a single injection may be sufficient In the usual causalgia injections must be repeated frequently enough to relieve the pain for several days before the causalgic syndrome begins to subside

This peculiar activity of TEA in the relief of pain is quite different from the physiologic effects observed during autonomic blockade, since the pain relieving action persists for some time after the other effects of an autonomic blockade have disappeared The relief of pain permits a patient to become ambulatory in instances of causalgia of the lower extremities without significant degrees of orthostatic hypotension and the mere demonstration of the ability to walk without the causalgic pain has tremendous psychologic benefits Relief of pain varies considerably from patient to patient depending upon the severity of the causalgic state and the patient's mental attitude Generally it will persist for 3 to 6 hours while the other evidence of autonomic blockade may only persist for 30 to 60 minutes Whether this is due to action of TEA on pain fibers peripheral to the ganglions or whether it is due to the ganglionic blocking action of the drug itself remains to be solved

Israel *et al* (65) have reported on the use of TEA for chest pain in 40 patients with relief in 25 The cause of the pain in this series included pulmonary infarction chest trauma pneumonia pleuritis tuberculosis neoplasm and mediastinal disease Berk (12) has used TEA for the amelioration of pain in pancreatitis if the patient was not in a shocklike state

Atkinson (8) treated 28 patients with angina pectoris with TEA 25 experienced significant improvement in their anginal status with an increased exercise tolerance test and decreased intensity of pain We too have observed that the pain of myocardial or pulmonary infarction may be relieved On the other hand the profound drop in blood pressure in certain elderly patients following intravenous use of these compounds makes it highly questionable whether such procedures are safe There is probably no contraindication to the use of the drug for the relief of chest pain in such conditions as pulmonary infarction trauma pneumonia and pleuritis in young people without evidence of arteriosclerosis

Cornbleet *et al* (25) have reported successful use of TEA to relieve itching from a wide variety of dermatologic disorders in which itching was a major cause of the patient's restlessness Obviously the skin condition was not altered but the patients were more comfortable

In a study of pain pathways in the herniated nucleus pulposus syndrome English and Spriggs (34) reported that they were able to relieve pain completely in 8 of 11 cases by intravenous administration of 0 3 Gm of TEA chloride in 2 cases pain was diminished and in 1 case there was no change During the 28 days of observation 2 patients were completely relieved of pain the others had a gradual return of pain but experienced relief again with a second injection

In Management of Gastrointestinal Disease The repeated demonstration that autonomic blockade is associated with a marked decrease in gastric secretion and in emptying of the stomach as well as in motility of the bowel has suggested that such drugs might be useful in the management of various gastrointestinal abnormalities associated with increased motility or increased acid secretion (31 66 84 121) It is interesting that administration of these drugs may immediately abolish the pain of peptic ulcer or the pain associated with gastrointestinal spasm Tetraethylammonium and the methonium compounds have a similar effect on these gastrointestinal activities provided they are given in sufficient doses These drugs will produce achlorhydria and will prevent the development of hyperchlorhydria following hypoglycemia However they may fail to prevent the hyperchlorhydria following the injection of histamine

These compounds may be of some use in the differential diagnosis of pain in the abdomen possibly arising from abnormal gastrointestinal motility The sudden cessation of gastrointestinal motility produced by intravenous administration of these compounds with its associated relief of pain may serve to explain certain abdominal complaints Not too much reliance should be placed upon this however for the general blockade of the autonomic nervous system will produce a considerable degree of relaxation in most patients and many patients will be relieved of their tension states (11)

Both types of compound have been used in an effort to manage peptic ulcer (84 101) Scott *et al* (101) administered 500 mg of hexamethonium at 8 00 A M 2 00 P M and 8 00 P M to 10 patients with duodenal ulcer The success of treatment was judged by a blind observer who also noted the effects on another group of 10 patients receiving intramuscular injections of potassium bromide Of the treated group 4 were judged to be greatly improved and symptom free and 2 continued to have mild symptoms In the control group none were symptom free Though these agents might be effective in the momentary control of ulcer symptoms the side reactions the orthostatic hy

potension and the general absence of autonomic tone make them unsatisfactory for long term management

Occasionally a patient with ulcerative colitis may have a significant decrease in the frequency of stools and the attendant discomfort associated with spasm and increased motility of the bowel following the injections of these compounds Tetraethylammonium is of no value in the relief of cardiospasm (84 87)

It is noteworthy that another quaternary amine banthine (beta diethylaminoethyl xanthene 9 carboxylate methobromide) has an atropine like action on cholinergic effector cells as well as some autonomic blocking action similar to that of TEA and the methonium compounds (58 71) This drug has a decided advantage over the other ganglionic blocking agents since it is practically as effective by mouth as it is parenterally Its action in man however is principally on the cholinergic effector cells and though the degree of autonomic blockade can be demonstrated by intravenous administration it is not as profound as that noted with the other compounds (117) It does not produce a significant degree of postural hypotension and will not prevent attacks of Raynaud s syndrome although it will mildly inhibit vasomotor reflexes in the digits Thus in moderate clinical doses at least the sympatholytic effects of banthine are minimal the parasympatholytic effects however are good probably due to the action on the cholinergic effector cells rather than on the ganglions

ADRENERGIC BLOCKING AGENTS

Other compounds are available which act directly on the effector cells of the sympathetic nervous system or which neutralize certain actions of epinephrine Thus clinically they may be said to have sympatholytic effect when the effector cell is modified or adrenolytic effect when the response to epinephrine is modified

Ergot Alkaloids

Crude or partially purified ergot preparations were the first agents to demonstrate specific adrenergic blockade (27 109) So much emphasis has been placed on the blocking property of these compounds that their other pharmacologic activities (smooth muscle stimulation and central nervous system depression) frequently have been overlooked with consequent misinterpretation of experimental and clinical

results The recent development of the hydrogenated ergots (116) (dihydroergotamine dihydroergocornine dihydroergocristine and dihydroergokryptine) with their attendant reduction in vasoconstrictor action has led to their use in hypertension However as previously implied the depressant effects on the central nervous system adequately explain the fall in blood pressure and decreased vasomotor reflexes in patients given doses known to be inadequate for the production of adrenergic blockade (16 44)

Dibenamine

A group of tertiary amines structurally related to the nitrogen mustards was first studied in the experimental animal by Nickerson and Goodman (88 89) Dibenamine (N N dibenzyl beta chloroethyl

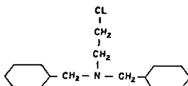


Fig 4

amine) (Fig 4) was shown to reverse the vasopressor response to epinephrine and to block the excitatory response of smooth muscle to sympathetic nerve stimulation and to epinephrine The drug provided protection against several times the L D 1 0 of epinephrine and almost completely prevented the cardiac irregularities elicited by epinephrine in dogs anesthetized with cyclopropane Dibenamine did not block the epinephrine induced cardiac acceleration or increased cardiac output Some evidence was also obtained that the drug might be effective in lowering the blood pressure of rats with experimental renal hypertension The authors concluded from their data that the adrenergic blocking effect of dibenamine was probably exerted on the effector cells to prevent the excitatory responses of epinephrine like substances

This sympatholytic drug was then studied by Hecht and Anderson (61) in 54 patients Intravenous administration was found to be the only route which was safe and gave consistent and predictable results The effective dose which could be tolerated was 4 to 6 mg per kilogram of body weight (0 25 to 0 50 Gm per patient) The drug was

diluted to at least 50 cc when given by slow injection or to 300 cc when given by infusion The latter mode of administration was preferred to avoid possible severe local damage due to leakage from the vein or to perivenous injection and because rapid intravenous injections had caused convulsions in animals The height of the pharmacologic action of a single intravenous dose occurred during the first 24 hours although some effects occasionally persisted for several days

Toxic reactions to dibenamine were frequent The irritating nature of the drug accounted for occasional pain along the arm during the infusion and one instance of thrombophlebitis The so-called "toxic effects" were nausea with or without vomiting drowsiness dizziness and an abnormal mental reaction (confusion perseveration and hallucinations) and convulsions in 1 patient with multiple sclerosis Certain "side reactions" such as nasal congestion and tingling of the feet were noted in a few patients and apparently resulted from interference with autonomic control in these areas

In the supine patient Hecht and Anderson noted a variable change in arterial pressure in both normal and hypertensive subjects When a fall in arterial pressure did occur it lasted for a few hours Peripheral vascular dilatation was also variable Skin temperatures of the extremities significantly increased in 4 of 9 patients with peripheral vascular disease Orthostatic hypotension was commonly observed usually maximal within 6 hours and lasting 1 to 2 days

Dibenamine blocked vascular responses to the cold pressor test in 11 of 15 subjects as well as the pressor activity of neosynephrine or epinephrine It also partially blocked the ectopic foci in the heart produced by epinephrine The effects of epinephrine on cardiac output peripheral blood flow respiratory volume and blood sugar were not particularly altered

On the basis of Cannon and Rosenblueth's (20) theory of sympathetic mediation and as a consequence of their own studies Hecht and Anderson have offered the following hypothesis with regard to the adrenergic blocking or sympatholytic actions of dibenamine Normally the mediator substance (*M*) released by the sympathetic nerve ending combines with a substance formed at the effector cell This latter hypothetic compound may be excitatory (*E*) or inhibitory (*I*) Thus the final active compound may be sympathin E (*ME*) or sympathin I (*MI*) Dibenamine (*D*) as well as other discussed sympatholytic agents may then compete with *E* for *M* and a resultant inactive substance (*MD*) formed The effective inhibitory substance (*MI*) would

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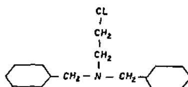


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present orthostatic hypotension precludes its use in ambulatory patients

In 1948 a patient with a pheochromocytoma was given dibenamine and responded with a rather dramatic fall in systolic and diastolic blood pressure (111) Shapiro *et al* (103) have more recently been able to repeat this effect in a proved case of pheochromocytoma While this might suggest the use of dibenamine as a therapeutic test for pheochromocytoma it is not of absolute diagnostic value since a drop in blood pressure in essential hypertension is also achieved The fact that this drug may eliminate the paroxysmal hypertension and associated symptoms in patients with a pheochromocytoma makes the drug of some value in the preoperative control of such patients

In the field of ophthalmology the therapeutic effect of this drug has been encouraging Christensen and Swan (22) gave dibenamine (4 5 mg /kg) intravenously to 18 consecutive patients with acute glaucoma of diverse etiology unresponsive to previously known medical measures There was no toxicity of note A dramatic reduction in ocular tension was recorded and the symptomatic relief was striking This action seemed unrelated to the pupillary and systemic circulatory effects of dibenamine nor was it blocked by local administration of mydriatic and cycloplegic drugs They believe that this agent may block the adrenergic ciliary body and thus prevent the formation of vitreous humor Bloomfield and Hasmovici (15) have employed the drug in 9 patients (18 eyes) with chronic simple glaucoma They noted an appreciable fall in ocular tension beginning 2 to 3 hours after administration and remaining at a relatively low level for periods ranging from 24 to 48 hours The therapeutic usefulness of dibenamine in chronic simple glaucoma appears to be in preparing these patients for surgery This adrenergic blocking agent may open a new therapeutic field and may provide needed information on the role of the autonomic nervous system in glaucomatous diseases

The fact that dibenamine blocks ectopic ventricular foci in animals and man suggests its use with cyclopropane anesthesia All concentrations of cyclopropane sensitize the myocardium to the arrhythmia inducing effect of adrenergic stimuli this strongly indicates that endogenous epinephrine or sympathetic nerve activity is involved in the spontaneous arrhythmias noted with cyclopropane anesthesia In experiments with dogs dibenamine in large doses (but not in small doses) gave practically complete protection against epinephrine induced arrhythmias in cyclopropane anesthesia (91) The protective

not be affected by this type of blocking activity of dibenamine

Since the report of these basic pharmacologic data on animals and man several reports speculating on possible therapeutic actions have appeared Haimovici and Medinets (57) gave dibenamine intravenously in average doses of 5 mg per kilogram to 18 patients with normal blood pressure to 6 with purely systolic (arteriosclerotic) hypertension to 7 with benign essential hypertension and to 7 with malignant essential hypertension Orthostatic hypotension occurred in both normotensive and hypertensive subjects A reduction to normal or below normal levels in supine arterial pressure was observed in benign essential hypertension The depressor effect started at the end of the infusion and lasted for 24 to 72 hours No noteworthy lowering of pressure occurred in the normotensive or systolic hypertensive groups The slight fall in pressure seen in patients with a malignant phase was regarded as insignificant The authors suggested the use of this drug in evaluating the neurogenic element of hypertension

Wunsch *et al* (118) studied 10 patients with malignant hypertension and 4 with severe benign hypertension After a control period of bed rest and barbiturate sedation dibenamine was administered intravenously The initial dose ranged from 2 to 5 mg per kilogram of body weight but depending on therapeutic response and toxic reactions subsequent doses were usually increased to 5 to 8 mg per kilogram A transient depression of supine blood pressure was observed in every case lasting from 1 hour to several days and averaging 24½ hours Upon averaging the maximal response of each patient a drop of 59 mm Hg systolic and 38 mm Hg diastolic pressure was found The decline in blood pressure was more prolonged and usually of greater magnitude than that produced by TEA A remission in hypertensive encephalopathy lasting from 3 days to several weeks occurred in 7 of 10 patients with malignant hypertension Diuresis and increase in urea clearance varied All alert patients experienced some toxic reactions The only clinical application suggested by these studies is the possible use of dibenamine as an accessory measure in hypertensive encephalopathy in an attempt to tide these patients over an acute episode Wunsch *et al* advise that the drug be reserved for patients failing to improve with standard medical measures

The same authors attempted to use enteric coated tablets of dibenamine but noted nausea and vomiting whenever a therapeutically effective dose was attained Dibenamine thus must be given intravenously and this fact together with the toxic reactions and the ever

present orthostatic hypotension precludes its use in ambulatory patients

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action is probably due to two factors (1) A direct cardiac action which requires larger doses of blocking agent than are necessary to reverse completely the peripheral pressor effect of the injected epinephrine (2) prevention of a rise in blood pressure (79 90)

Nickerson and Brown (86) studied dibenamine preoperatively in 20 healthy young adults undergoing elective surgery with unsupplemented cyclopropane anesthesia In 7 used as controls "spontaneous arrhythmias occurred in all planes of anesthesia and increased as the depth of anesthesia increased Ominous ventricular rhythms were exhibited by these 7 patients in plane 4 and stage IV Preoperative administration of dibenamine in doses of 5 to 6 mg per kilogram caused only slight reduction in the incidence and severity of the arrhythmias in 7 patients whereas 7 0 to 7 5 mg per kilogram almost completely eliminated all arrhythmias in 6 others Only minimal reactions to the drug were seen and this was attributed to prior sedation with barbiturates Although further clinical experience is indicated it would seem that dibenamine may be of value in extending the application of this anesthetic agent

Dibenamine has recently been reported to produce marked relaxation of the gastroesophageal junction and rapid emptying of the esophagus in a case of cardiospasm (87) This tends to confirm the thesis that relative or absolute sympathetic overactivity at the effector cell is responsible for this condition since cardiospasm is not affected by ganglionic blockade with TEA

Dibenamine is one of the more effective adrenergic blocking agents available for clinical use although the rather frequent side effects and the mode of administration limit its usefulness However a large number of congeners of dibenamine has been synthesized and studied pharmacologically (85) and it is hoped that one or more of these will prove to be sufficiently well absorbed after oral administration to permit their use

BENZODIOXANE AND RIGITINE

Fourneau and Bovet (39 40) and Bovet and Simon (17) some 18 years ago investigated the properties of the benzodioxanes and demonstrated in animal experiments that 933F (2 piperidinomethyl 1 4 benzodioxan) (Fig 5) has both adrenolytic and sympatholytic effects With increasing dosage it first decreases then abolishes and finally reverses the hypertensive action of epinephrine on blood pres

sure This adrenolytic response occurs in doses ranging from 0 25 to 2 mg per kilogram whereas more than 10 mg per kilogram is necessary to elicit a peripheral sympatholytic action This sympatholytic dose definitely approaches the L D_0 limit (the maximal tolerated dose) Thus only 1/40 to 1/80 of the sympatholytic dose is required to produce a significant depression of hypertension due to epinephrine

It appears that at high dosage levels 933F (benzodioxane) has a mode of action similar to dibenamine However at smaller dosage levels the property of benzodioxane to neutralize the effects of injected epinephrine is greater Morison and Lissak (80) have shown *in vitro* that epinephrine is inactivated about three times more rapidly in solu

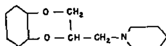


Fig 5 —Chemical structure of benzodioxane

tions containing benzodioxane than in solutions containing epinephrine alone It is known that epinephrine destruction is much more rapid in living tissue than when studied *in vitro* These authors consider it probable that doubling or tripling of the rapid rate of epinephrine destruction in the tissues would definitely alter the maximal concentration possible at a given time after its injection Although the exact mechanism of benzodioxane s adrenolytic action is not clear such a direct inactivation of epinephrine seems very plausible

It is evident that the therapeutic application of this drug is limited to its effects in neutralizing circulating epinephrine Goldenberg *et al* (51) attempted to produce pharmacologic sympathectomy in essential hypertension but discovered that in tolerable doses benzodioxane was adrenolytic only However they were able to devise a test for pheochromocytoma (49) the only disease state so far known to be due to circulating epinephrine This tumor which occurs in the adrenal medulla or in any one of the widespread areas where chromaffin tissue is found during early life has been thought of as a rarity Smithwick in 1 000 hypertensive patients subjected to lumbodorsal sympathectomy *during which both adrenal glands* were exposed found an incidence of 0 5 per cent But with the advent of the benzodioxane test a rather surprising number of 59 cases of pheochromocytoma has been recorded (49) In many clinics it is now the practice to investigate each hypertensive patient for the presence of a pheochromocytoma

The benzodioxane test is performed with the patient supine and with a slow intravenous drip of isotonic saline running into one arm through a three way stopcock After the blood pressure and pulse have stabilized 10 mg of benzodioxane per square meter of body surface (0 25 mg/kg) is given over a 2 minute period Blood pressure and pulse determinations are taken at frequent intervals for the next 15 to 20 minutes Initially Goldenberg *et al* employed this test on 58 subjects 4 patients who later were proved to have a pheochromocytoma demonstrated an immediate and impressive drop in blood pressure over a period of several minutes This type of reaction was not seen in 28 patients with hypertensive disease of diverse etiology In 14 normal subjects the drug had a mild transitory pressor effect They also performed 15 epinephrine infusions the rate of which was adjusted to increase the systolic blood pressure by approximately 25 per cent In every case the fall in blood pressure following the injection of benzodioxane after epinephrine approximated in magnitude the rise induced by epinephrine alone Baker (10) has been unable to demonstrate depressor effects in 30 patients with hypertension used as controls Grimson *et al* (54) and Dana and Calkins (29) have had similar experiences with benzodioxane The absence of depressor response to benzodioxane in control subjects with hypertension lends a degree of specificity to this test in pheochromocytoma

The normal adrenal medulla and pheochromocytomas have now been shown to contain not only epinephrine but also varying amounts of arterenol (nor epinephrine) (50 63) The demonstration that benzodioxane has the same depressor effect on circulating nor epinephrine as on epinephrine has been accomplished by Goldenberg *et al* (50) and by Melville (77)

Goldenberg and Aranow (49) described 3 cases of pheochromocytoma with persistent hypertension and negative response to the benzodioxane test They postulated that at the time the test was performed the hypertension was no longer due to circulating epinephrine or nor epinephrine but that the previous presence of these compounds in excessive amounts for a considerable period had set into operation a secondary mechanism This view is supported by the fact that 7 of 12 patients with pheochromocytoma remained hypertensive for varied lengths of time after operative excision of the tumor Mason (74) has recently recorded one false negative" and one equivocal result of the benzodioxane test in 2 proved cases To date false positive" reactions have been recorded in 10 cases (33 46 48) It is interesting that in

all of these cases of hypertensive vascular disease uremia was present However Snapper (108) reports that he has observed "false positive" responses in hypertensive patients without uremia Further study will determine whether hypertensive patients in uremia limit the usefulness of this test

Apgar and Papper (6) have reviewed 91 cases of pheochromocytoma in which surgical treatment had been undertaken One of the serious problems in the anesthetic management of these cases arose from the physiologic effects of excessive secretion of epinephrine and nor epinephrine during the procedure They employed benzodioxane infusions repeatedly and with benefit to control the paroxysmal hyper tension They preferred benzodioxane to dibenamine because of the rapid action of the former

While the clinical usefulness of benzodioxane is limited this should not deter its proper application A pheochromocytoma does not pro duce a typical clinical picture Discovery of the tumor should be con sidered imperative since removal will often cure the hypertension Since the benzodioxane test is useful in pheochromocytoma only when the blood pressure is elevated the injection of certain "pressor" agents such as histamine (93) mecholyl (56) and TEA (67) is indicated in the normotensive patient in whom pheochromocytoma is suspected Histamine and mecholyl induce a pressor response probably by a direct stimulating action on the adrenomedullary tissue (35) Tetra ethylammonium also has this direct action but in addition there is the loss of a compensatory mechanism to circulating epinephrine which occurs after total ganglionic blockade (35 78) However the observed pressor response is not specific and only becomes so when benzodiox ane can nullify or abolish the reaction

Grimson *et al* (33 54 70) have introduced C 7337 or regi tine (2 N p tolyl N [m hydroxyphenyl] aminoethyl imidazoline hydro chloride) as an adrenolytic agent The slightly more pronounced and definitely longer lasting reductions of blood pressure following administration of 5 mg of regitine intramuscularly or intravenously were readily recognized in 4 patients with pheochromocytoma In 62 patients with hypertensive vascular disease the fluctuation of blood pressure following regitine was less than following benzodioxane This new drug too gave "false positive" reactions in the presence of uremia Their studies confirm the value of the benzodioxane test They also in dicate that the results of the regitine test compare favorably with those of the benzodioxane test and may be preferable for routine use be

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like properties were demonstrated in the rabbit by coronary constriction and increased arterial pressure and in the dog by stimulation of the isolated gut and uterus None of these histamine like properties could be prevented by atropine Finally the pressor action of epinephrine in the experimental animal could be blocked and occasionally reversed by priscoline Thus the compound possesses sympathomimetic histamine like acetylcholine like sympatholytic and adrenolytic properties This diversity of activity merely serves as a maze for the practicing physician although to the pharmacologist it may be a valuable tool

We have included priscoline in this review primarily because it is employed clinically as an effective vasodilator in neurogenic vasospastic syndromes In our opinion the peripheral vasodilatory effects of priscoline as observed clinically are similar to those of histamine The sympatholytic and adrenolytic properties are probably of minor importance Reference has already been made to the structural formula and its resemblance to histamine Siems and Rottenstein (104) have utilized a cross circulation preparation on dogs to differentiate between the actions of the drug mediated by the vasomotor nerves and local vasodilating actions They clearly demonstrated that priscoline has only a local action Avera *et al* (9) have determined that priscoline induces a twofold increase in blood flow in the sympathectomized extremity as measured by the venous occlusion plethysmograph Again priscoline resembles histamine in the latter s direct nonadrenergic dilatation of blood vessels

Epinephrine has long been known to be a physiologic antagonist to certain effects of histamine and will prevent or counteract most symptoms if administered quickly The so called adrenolytic effect of priscoline could very well represent a histamine like antagonism to epinephrine Whether the pressor reaction of epinephrine would be abolished or reversed would then depend on the pharmacologic dosage preponderance of priscoline over epinephrine Studies are now needed to determine whether or not antihistaminic agents can appreciably modify priscoline activity on peripheral blood vessels This discussion was not undertaken to discourage the therapeutic application of priscoline but to point out how the understanding and classification of this drug may be inaccurate

Priscoline may be administered orally intramuscularly intravenously and intra arterially The oral dose varies from 75 to over 400 mg daily in divided doses Intramuscularly or intravenously 25 to 75

cause of the simplicity and easily recognized long lasting hypotension (1 to 3 hours) when the response is positive

PRISCOLINE

The pharmacodynamic properties of priscoline (2 benzyl 4 5 imidazoline hydrochloride formerly known as priscol) have not been definitely established The action of priscoline is very complex and even though the drug is often regarded as possessing over all adrenolytic or sympatholytic activity such an assumption may be erroneous A glance at the chemical formula reveals a structural relationship to both the

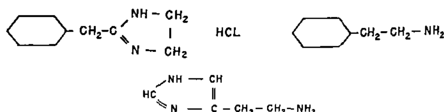


FIG 6—Chemical structure of priscoline (above left) phenylethylamine (above right) and histamine (below)

sympathomimetic amines (e g phenylethylamine) and histamine (Fig 6) Certain chemical modifications of the priscoline structure will produce an active sympathomimetic agent privine (26) or histamine *Does this basic chemical similarity between compounds indicate priscoline s main pharmacologic activity?*

Many reports on priscoline of an experimental nature appeared between 1939 and 1943 in the European literature They noted reduction in blood pressure (59) vasodilatation (76) certain adrenolytic action (75 81) stimulation of gastric motility (52) and abolition of the temperature gradient of the extremities with resultant increased temperatures of the fingers and toes (68) Later Ahlquist *et al* (4 5) in this country attempted further definition They found a rather generalized vasodilatation which was felt to be due to sympathomimetic action similar to that of other sympathomimetic substances including ethyl epinephrine and ethylnorsuprarenin Cardiac stimulation and increased cardiac output resembled sympathetic stimulation such as is seen with epinephrine The principal action of priscoline on the gastrointestinal tract was stimulation and this could be prevented with atropine Yonkman *et al* (120) have also reported this cholinergic action Histamine

blood flow Wakim *et al* (116) gave 50 mg of priscoline intravenously to 10 subjects without peripheral vascular disease By means of the venous occlusion plethysmograph the combined average increase in blood flow in both forearms at 5 15 30 and 45 minutes respectively after injection was found to be 89 0 60 5 48 5 and 46 0 per cent Comparable figures were also recorded for both legs In a few patients in whom the blood flow was determined 3 to 5 hours after the drug was given the increase was maintained They concluded that the effects on peripheral blood flow were not marked but that they might last a few hours Murphy *et al* (82) employed the same methods but in addition determined the removal of radioactive sodium from the gastrocnemius muscle following administration of 25 mg of priscoline in 10 normal subjects The immediate mean increase in blood flow was 59 per cent but after 5 minutes no increase was observed in any instance Of 9 subjects the rate of sodium removal was significantly decreased in 6 unchanged in 2 and significantly increased in 1 This finding is very similar to the effect of sympathetic block and sympathectomy on the rate of sodium removal The results therefore indicate that skin and subcutaneous blood flow is increased at the expense of muscle blood flow possibly by some shunting process

This drug is being widely used in the treatment of peripheral vascular disease Grimson *et al* (55) have been very encouraged by their results in Raynaud s syndrome vasospastic ischemic extremity and some causalgic states Results in Raynaud s syndrome have been so successful that they no longer recommend sympathectomy We have found that if patients can tolerate individual doses of 50 to 100 mg of the drug orally it is an effective means of controlling the symptoms On the other hand Grimson *et al* noted that the benefit in organic arterial disease was not so striking and they were unable to demonstrate any uniform change in oscillometric readings despite the increased or abolished temperature gradient Priscoline 75 mg intravenously was recommended as a test to aid in predicting the immediate results of sympathectomy Because of our belief that this drug has only a local histamine like vasodilatory property we seriously doubt the value of such a test

In 10 patients with arteriosclerotic peripheral vascular disease Rogers (97) reported rather uniform improvement of *intermittent* claudication Ulcerated lesions seemed to heal more readily and oscillometric readings were improved The same short term benefit was seen in 4 cases of thromboangiitis obliterans Symptomatic remissions

mg every 4 to 6 hours is often given although larger doses have definitely been reported In the case of sudden occlusive arterial disease an intra-arterial injection of 25 to 50 mg would be an average dose and this may be repeated as indicated In any event the optimal dose varies from patient to patient hence therapy must be strictly individualized

Often the optimal therapeutic dose will not be attained because of the appearance of undesirable reactions which occur in about 25 to 30 per cent of patients Following priscoline administration there is often a flushing of the skin and an appearance of "goose flesh as well as a feeling of chilliness More disturbing are the apprehension mental excitation formication nausea vomiting dizziness orthostatic hypotension palpitation headache and a stuffy nose Gastric hypersecretion is a common effect and Nasio (83) has used priscoline as a substitute for the standard histamine test This certainly implies cautious application in the patient with a peptic ulcer The nausea and vomiting have reportedly been lessened by the addition of cholinergic blocking agents such as atropine and belladonna (120) but this has not been our experience Recently the interesting observation has been made that in some diabetic patients the blood sugar is lowered to a degree necessitating material reduction of insulin dosage (119)

Priscoline therapy has caused exacerbation of coronary insufficiency Yonkman (119) has postulated that this might be due to either of two factors (*1*) a redistribution of available blood into dilated areas away from an already embarrassed myocardium or (*2*) a direct cardiotonic effect of priscoline as evidenced by palpitation and increased cardiac output Flasher *et al* (38) have studied the electrocardiographic pattern following intravenous injection of priscoline in 13 patients and found several instances of auricular premature complexes altered T wave amplitude and ST segment depression There was 1 instance of ventricular tachycardia Because of the lack of correlation between the electrocardiographic and systemic effects of priscoline they assumed that the altered electrocardiographic pattern represented a direct myocardial effect

Whether or not therapy should be continued in the presence of undesirable reactions can be decided only on the basis of the severity of the disease the noxiousness of the reactions and evaluation of the anticipated results and efficaciousness of the drug To date no deaths attributed to priscoline have been reported

In an effort to define more exactly the extent of increased peripheral

Because acute cerebral accidents might have an element of associated vasospasm Prandoni and Alpert (94a) have injected 3 to 6 mg of priscoline into the carotid artery on the affected side with beneficial results Some scattered reports of such benefit after oral or intravenous administration can now be found in the literature (119) but this therapy is not yet on firm ground In the hypertensive states the blood pressure response has been so very minimal and variable that most workers have now abandoned any thought of a therapeutic approach

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were induced in 2 cases of causalgia and 1 of trench foot Frank *et al* (42) studied a group of 22 patients and contrary to their expectations obtained fairly good results in 15 arteriosclerotic individuals Good results were also reported in 3 cases of thromboangiitis obliterans with either large oral or relatively large intravenous doses In contrast, Flasher *et al* (38) who have been evaluating the oral administration of priscoline in moderate to severe arterial disease find that patients with arteriosclerosis obliterans do not show dramatic benefit insofar as intermittent claudication and ischemic rest pain are concerned They believe that only after a long term study can any opinion be offered regarding the survival of the affected extremity

Clinically priscoline has given encouraging results in the treatment of peripheral vascular disease especially patients having a known vaso spastic element The reports so far note few alarming undesirable reactions This coupled with the several modes of administration that priscoline permits gives the compound an advantage over the other agents previously discussed Priscoline does moderately increase the total blood flow to the extremities but the present methods of study do not accurately differentiate between nutritional and so called arteriovenous shunt flow The ultimate advisability of employing a drug that produces generalized vasodilatation remains unsettled in much the same way as that of the ganglionic blocking agents

Smith *et al* (107) have been impressed by the occurrence of lesions in the sympathetic ganglion and internuncial and intermediolateral cell groups of the spinal cord and brain stem in the acute phase of polio myelitis They believe that this is an anatomic explanation for vasomotor disturbances ischemic pain and other evidences of sympathetic instability so common in acute poliomyelitis Because of priscoline's assumed sympatholytic properties they have given the drug in rather large doses to 602 poliomyelitis patients with subjective pain objective muscle tenderness arterial tenderness muscle spasm or any combination of the foregoing signs or symptoms (106) "Nearly all patients manifested some form of progress and their clinical status improved so rapidly that it was possible to transfer the majority of them relaxed and free of pain to their homes or to orthopedic hospitals in 7 to 14 days Even though the optimal dose was determined by the appearance of flushing the undesirable effects of priscoline were apparently not marked enough to preclude further therapy Geisler *et al* (47) observed no benefit from this type of vasodilating therapy but Polley (94) achieved results with priscoline equal to those obtained with the hot pack method

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Aspects of the Influenza Problem

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VIROLOGY AND EPIDEMIOLOGY

THE CLINICAL differentiation of influenza from other acute respiratory diseases remains vague Uncomplicated influenza is an acute epidemic infectious disease of 2 to 4 days duration The principal signs are nasopharyngitis and nonmucopurulent tracheobronchitis often associated with bacterial inflammation of the paranasal sinuses middle ear bronchi and lungs Human influenza virus was discovered in 1933 by Smith *et al* who introduced the ferret as an experimental animal (70) Great progress has been made since then and influenza can now be defined as an epidemic infectious illness caused by an epitheliotropic virus which invades the mucosa of the respiratory tract Virologic studies have shown that subclinical influenza infections occur frequently

The electron microscope reveals that the old mouse adapted laboratory strains of influenza virus are spherical particles of about 90 to 105 mμ in diameter This however is not true of all influenza virus strains Recently Chu *et al* (17) have shown that freshly isolated egg strains of the A group consist in part of long filamentous forms which can easily be seen in the darkfield microscope

ANTIGENIC VARIATIONS OF VIRUS STRAINS At present three groups of human influenza virus can be distinguished These groups designated A B and C are antigenically different from each other Within the A and B groups there are a great variety of strains The human

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fluenza A epidemic in Europe in the winter of 1948-49 originated in one focus and from there spread to other countries Far more detailed investigations however will have to be carried out particularly with respect to the primary focus Blind spots in undeveloped countries are a particularly great drawback to success of such investigations

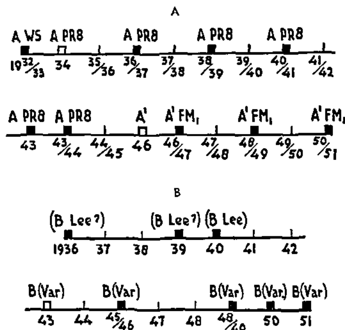


Fig 1—Major epidemics of influenza in the Northern Hemisphere 1932-51 Influenza B tends to appear later in the winter than influenza A (A') A epidemics of influenza A Solid blocks epidemics of influenza A and A' Open blocks isolation of strain A PR8 in Puerto Rico (1934) and the first strain of A' (CAM) in Victoria Australia (1946) B epidemics of influenza B Open block isolation of Bon strain in Melbourne (1943) an antigenic variant Parentheses influenza B diagnosed on serologic evidence

The pig may carry the virus in a masked form in lungworms which are a source of infection for other pigs via earthworms (69) No comparable intermediate hosts of the human influenza virus are known and the movements of the virus between epidemics are obscure (2) So far no human carriers of influenza virus have been identified with certainty although during epidemics the virus has been recovered from throat washings of apparently healthy individuals

A group can be subdivided into the subgroups A WS A PR8 and A′ FM1 This subdivision is a provisional one (83) Swine influenza virus discovered in 1930 by Shope is antigenically related to the A group but differs from the human A strains The A WS strain (WS are the initials of the patient from whom the virus was obtained) was discovered in 1933 in London but has since been of no epidemiologic importance The A PR8 strain discovered in 1934 by Francis (27) in an influenza epidemic in Puerto Rico was regularly recovered between 1934 and 1943 in influenza epidemics in various parts of the world Anderson and Burnet (1) isolated a new strain in Victoria in 1946 which proved to belong to a new subgroup provisionally called A′ The strain FM1 which was isolated in 1947 by Rasmussen *et al* (62) belongs to the A′ subgroup The influenza epidemics in America and Europe in the winters of 1946-47 1948-49 and 1950 51 were caused by this subgroup The old A PR8 group has probably disappeared since 1943 (46a) Every 2 years influenza A (A′) virus causes wide spread winter epidemics in different areas although it cannot be pre dicted which country will be affected or which area will remain free Our knowledge of sporadic interepidemic and endemic cases is con stantly widening

The epidemiology of influenza B is much less clear The antigenic composition of the B strains is still being investigated It is almost cer tain that the first representatives of the B group discovered in 1940 by Francis (25) and by Magill (51) have been replaced by a serologic variant (6a 7 16 81) One of the first known representatives of this variant was the Bon strain isolated by Beveridge *et al* (6) in Mel bourne in 1943 Epidemics of A and B influenza may occur simulta neously and sporadic cases of influenza B may be observed during widespread epidemics of influenza A (A) The epidemiologic im portance of "C" influenza has not yet been adequately established (31) The principal epidemics of influenza A and B that have been recorded in the Northern Hemisphere since 1933 are graphically presented in Figure 1

Two theories have been proposed with regard to the origin of epi demics (*1*) Influenza tends to break out in several countries simul taneously depending on seasonal factors which prevail from November to April in the Northern Hemisphere (*2*) Influenza appears in one area and is conveyed elsewhere by contact infections An investigation of this extremely complex question was started in 1947 with the aid of the World Health Organization (16 46a 77) Almost certainly the in

ferret with unfiltered sputum or washings or after mixing with antibiotics by inoculation into the amniotic cavity of 13 day old embryonated eggs The latter procedure permits the virus to gain entry into the epithelium of the parabronchi of the chick embryo The amniotic fluid is collected after 3 days and subsequent passages are performed in the allantoic cavity Strains of influenza B virus are often avirulent for ferrets and should be isolated with the chick embryo technic

For the hemagglutination test the amniotic fluid is diluted 10 to 20 fold A positive result indicates that virus has been grown in the chick embryo Serologic classification supplies further proof that an

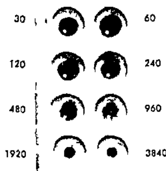


FIG 2—Quantitative hemagglutination test (43) with twofold dilution of influenza virus containing allantoic fluid and chick n red cells showing pattern of hemagglutination and sedimentation The titer of allantoic fluid is 480 four plus using 0 5 per cent in final dilution of the red cells

influenza virus has been recovered This is performed by means of the hemagglutination inhibition test with virus from the first positive amniotic fluid provided the titer is sufficiently high For this purpose the nonspecific inhibition of the specific antiserums must be removed The required specific antiserums are prepared by immunizing ferrets rabbits or roosters Among the "specific diagnostic antiserums now available are anti A WS (1933 England) anti A PR8 (1934 U S A) anti A' FM1 (1947 U S A) anti B Lee (1940 U S A) and anti B Bon (1943 Australia) The complement fixation test with plain amniotic fluid is not as suitable for strain differentiation as the hemagglutination inhibition test because the former is insufficiently specific to elicit a sharp differentiation of the subgroups within the A or B group

VIROLOGIC CONFIRMATION OF CLINICAL DIAGNOSIS Influenza cannot be diagnosed clinically with absolute certainty in individual cases

It is still unknown why the influenza viruses apparently change their antigenic composition Presumably in 1933 we were at the tail end of the epidemics of the A WS type The subgroup A PR8 evidently maintained itself for about the next 10 years after which the antigenic variant A′ made its appearance The following hypothesis has been proposed to explain this phenomenon After a certain strain type of the virus has caused epidemics for a number of consecutive years antigenic mutants may appear under the influence of a continuous increase in group specific antibodies in the world population So far however no experimental data support this hypothesis

Many epidemiologic observations cannot be explained at present In the winter of 1947 a limited epidemic caused by the "new" A′ virus occurred in the Netherlands Nevertheless in 1949 antibodies against this strain were not generally present and that winter the strain caused an extensive epidemic there About 1 000 000 persons—10 per cent of the country s population—were ill and some 2 200 individuals died of influenza in 2 months The virulence or perhaps the stage of adaptation may therefore well be an important characteristic of the virus Unfortunately neither factor can as yet be determined with any degree of certainty for man (69a 71a)

Laboratory Technics The laboratory identification of influenza virus infections has been so simplified by the work of a number of investigators (5 43 50) that most clinical laboratories are able to perform it correctly Present serologic methods for demonstrating influenza antibodies in the serum are based on the complement fixation procedure or on the hemagglutination inhibition test using egg fluids containing the virus as antigen The latter method is based on the property of the virus discovered by Hirst (43) and by McClelland and Hare (50) to cause agglutination of the red blood cells of the chicken guinea pig or man (Fig 2) In our opinion the complement fixation test is preferable for routine work since the technic is familiar to most laboratories Moreover a complicating factor in the hemagglutination inhibition test is the nonspecific binding of serum mucoproteins by the influenza virus especially when recently isolated strains which have been passed only in eggs are employed as antigens This sometimes prevents the demonstration of a slight postinfectious rise in antibody titer

The nonspecific inhibition in serum can be completely neutralized with enzymes of Vibrio cholerae (13 83)

Strains of influenza virus A are isolated by nasal inoculation of the

titer must be at least 3 000 or higher since many persons show a rather high anamnestic titer for years after an influenzal infection In such cases the diagnosis can only be made if a continuous fall in the anti body titer can be demonstrated during the months following the dis ease (Fig 5) All monthly serum samples should therefore be pre served if such comparative tests are to be performed If the patient dies of influenzal pneumonia within 5 days of onset of the illness the

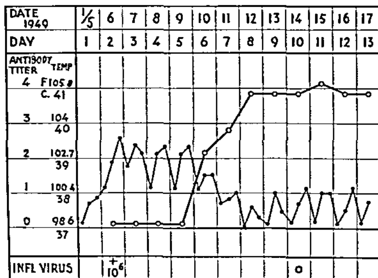


FIG 4—Rise of influenza virus A antibody titer in the blood serum in a case of influenza associated with chronic mucopurulent bronchitis and bronchiectasis H influenzae was found in the mucopurulent sputum The virus was isolated from the sputum in high concentration Curve with solid dots temperature curve with circles log antibody titer

virus is isolated from the sputum tracheal mucosa or lung tissue (at autopsy) Sputum obtained bronchoscopically from the trachea after death may also be used

MORTALITY By far the greatest mortality is due to secondary bac terial pneumonias In epidemics of A or A influenza the figures are still alarmingly high No fatal cases of influenzal encephalitis are known The latter possibility however should be taken into account since some strains of influenza virus have been rendered neurotropic for the chick embryo and the mouse (78) The statistics from various countries on influenza mortality are comparatively much the same The

Virus isolation when performed as described above may confirm the diagnosis in 3 to 5 days A good source for virus isolation is the patient's sputum the virus is often present there in high or extremely high concentration (up to 10^7 M I D_{50} per milliliter) When no sputum is available the patient is instructed to expectorate mucus from the nasopharynx into a sterile receptacle he is then asked to gargle with a mixture consisting of equal parts of nutrient broth and sterile physio

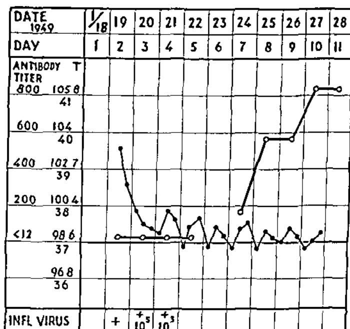


FIG 3 —Rise of influenza virus A antibody titer in the blood serum in uncomplicated case of influenza The causative virus strain was isolated in high concentration from gargling Curve with solid dots temperature curve with circles *antibody titer*

logic saline Both sputum and washings should be sent to the laboratory on ice to maintain virus viability Isolation of strains is possible up to 4 or 5 days after onset of the illness Demonstration of the rise of antibody titer against strains of influenza virus requires more time The rise does not start until 5 or 6 days after onset of the disease (Figs 3 and 4) The maximal titer is reached in 2 or 3 weeks after which the titer decreases slowly for several months Only a very high antibody titer is considered conclusive evidence in influenzal pneumonia when patients come under observation late in the course of their disease The

thelium being formed After 21 days this newly formed epithelium had for the most part differentiated into normal ciliated respiratory epithelium These experimental data provide strong evidence that the influenza virus grows in the epithelial cells of the respiratory tract but not in the undifferentiated basal cell layer

Similar epithelial lesions have in recent years been observed in the trachea and bronchi in human influenza (41 55 76) (Fig 6 A F) It is difficult to study these lesions in man since in almost all cases the mucosa of the respiratory tract shows secondary bacterial infection (often with Staphylococcus aureus) In 1 of our cases (42) however the bacterial infection produced by pneumococcus type 3 and Hemophilus influenzae did not involve the tracheal mucosa In this case therefore there may well have been a pure lesion of the tracheal mucosa due to the influenza virus (Fig 7A) The epithelial lesions may be diffuse or confined to local areas in the mucosa (41) The submucosa shows a considerable mononuclear infiltration and hyperemia These findings confirm those of Winternitz *et al* (85) and Askanazy (4) in the 1918 influenza epidemic Perhaps it may be possible to demonstrate influenza virus in the necrotizing epithelium by means of the electron microscope

As demonstrated by Straub (76) epithelial destruction in influenza can be properly judged only if autopsy is performed as soon as possible after death Particular caution must be taken not to open the air passages during autopsy for when the trachea and bronchi are cut open and the inner surface is washed out epithelial artefacts make it impossible to recognize the specific lesions Trachea and lungs should be removed *in toto* and small sections cut from these organs with a very sharp sterile knife for virologic and bacteriologic study Trachea and lungs are then fixed *in toto* the lungs first having been incised in a few places in a direction perpendicular to the stem bronchus Only after a few days should portions be removed for microscopic examination

The epithelial destruction in the trachea and bronchi is so characteristic that a rapid tentative postmortem diagnosis of influenza can be made by cytologic smears of the tracheal or bronchial epithelium (42) (Fig 7) The possibility that epitheliotropic viruses other than influenza may give rise to the same lesions must always be borne in mind Cytologic smears of the patient s sputum also reveal clearly the epithelial desquamation and degeneration It would be interesting to determine whether smears of the epithelium of the nasal mucosa might

mortality statistics for Holland for the years 1916 through 1951 show that except for the second wave of the great pandemic in the autumn of 1918 the older age groups suffered the highest mortality This seems to be the rule for most recorded influenza epidemics The enormous fatality of the second wave of the 1918 epidemic in which the age group from 20 to 40 years suffered severely is probably unparalleled

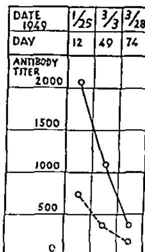


FIG 5 —Influenza virus A antibody titer from a case of staphylococcal pneumonia during the 2 months following the disease proving that the pneumonia was secondary to influenza Solid line influenza A antibody titer broken line influenza A antibody titer (one experiment)

in the history of influenza The many theories proposed offer no satisfactory explanation for it

HISTOPATHOLOGY

EPITHELIAL NECROSIS IN THE RESPIRATORY TRACT IN FATAL CASES Straub (74 75) demonstrated that in mice influenza virus caused necrosis of the ciliated and the goblet cells of the tracheal and bronchial epithelium Regeneration of new epithelium starts from the basal layer of cells which remain intact This was also described by Francis and Stuart Harris (29) for the nasal mucosa of the ferret they found that the ciliated and the goblet cells had disappeared 2 days after intranasal infection and that only the basal cell layer remained Regeneration started 4 days afterward a few layers of undifferentiated epi

supply a basis for the diagnosis during the course of the influenza

How far the epithelial lesions descend into the bronchial tree is unknown The interlobular bronchioles were not involved in one series of cases (76) Hers (41) found necrotic lesions in the epithelium of the interlobular bronchioles which were probably initiated by the influenza virus in 1 of his cases Detailed knowledge however is still lacking

INFLUENZA VIRUS PNEUMONIA After a number of intranasal passages of influenza virus A in anesthetized ferrets the animals die with nonbacterial pneumonic consolidation attributable to the influenza virus itself In the same way A and A strains of influenza virus from ferrets or chick embryos may be adapted to the mouse lung so that after a certain number of passages the mice die and show the same pneumonic picture as the ferret Fatal viral pneumonia may be caused in this way by high dilutions of some virus strains (for example a dilution of 10^{-5} of a 10 per cent emulsion of infective mouse lung) The histologic picture of influenza virus pneumonia consists of hemor

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FIG 6—Case of influenza A with patchy fibrinopurulent tracheobronchitis and extensive bronchopneumonia in the right lung due to Staph aureus The patient 27 died 3 days after onset of influenza At autopsy a strain of influenza virus A was isolated from the trachea The lesions (A–F) may be considered injury to the epithelium by the influenza virus there is no apparent bacterial inflammation and the lesions are identical with those produced in experimental animals by the influenza virus (55)

A normal ciliated respiratory epithelium from left side of tracheal bifurcation with some lymphocytes between epithelial cells Regular nuclear arrangement with long axes of basal and other nuclei perpendicular to basement membrane No hyperemia and little mononuclear infiltration (×225)

B loss of structure of tracheal epithelium at bifurcation Irregular position and degeneration of nuclei swollen protoplasm distinct intercellular edema Basement membrane swollen with edema under basal layer of epithelial cells Hyperemia and hemorrhage in mucosa (×225)

C partial desquamation of necrobiotic epithelium at bifurcation Hemorrhage between basement membrane and epithelium hyperemia and mononuclear infiltration of mucosa (×225)

D considerable necrobiosis of respiratory epithelium at bifurcation only the basal cell layer remains nuclei of which are round or oval and have their long axes parallel with surface of the epithelium Mitosis in vertical direction Hemorrhage under the epithelium (×225)

E mucosa from bifurcation Epithelium shows only one or two rows of nuclei *the upper row of cells is often considerably flattened* Severe hyperemia of mucosa (×225)

F mucosa from bifurcation Epithelium of duct in center of field shows changes similar to those in trachea To left of field shown there was an epithelial defect with fibrinopurulent exudate (see Fig 8) some of which is visible in the tracheal lumen (×75)



FIG 6 — Legend on facing page

Virus can usually be isolated from peripheral portions of lung tissue of persons who have died of pneumonia soon after onset of the influenza—sometimes even in very high concentration (53 57) Should such cases be looked upon as influenza virus pneumonia associated with bacterial infection? This question cannot be answered since pulmonary lesions due to influenza virus cannot be recognized in the presence of bacterial infection

Straub (75) and Taylor (82) showed that nonfatal concentrations of influenza virus in mice may cause fatal viral pneumonia when the animals are made to aspirate saline (or normal serum) a few days after the intranasal infection Jones (49) noted that an influenza B egg strain could easily be adapted to the mouse lung if together with the virus the mice were made to aspirate dead or living bacteria or such substances as powdered glass or starch In man the influenza virus is often present in high concentrations in the nasopharynx and bronchial exudate (44 57) so that aspiration of the contents of the air passages antemortem is apt to transfer a large quantity of the virus to the lung parenchyma These observations suggest that aspiration and secondary irritation" in the lung will promote the recovery of the virus from the lung tissue This may explain why influenza virus may be found in the human lung even if the strain does not manifest a clearly primary pneumotropic character

Did the prevailing virus in 1918 have a strong human pneumotropic affinity? Certain postmortem observations made at that time seem to suggest it (35 84 85) This theory is the simplest explanation of the numerous bacterial superinfections during the second wave of the epidemic that year It would permit the assumption that the virus had adapted itself to the human lung in contrast to a presumed lack of adaptation during the first wave

INITIATION OF CELLULAR INFECTIONS BY INFLUENZA VIRUS The histopathology of influenza seems to indicate that the virus gains entry into the epithelium of the respiratory tract and subsequently destroys it Recent studies (10 11) suggest that mucoproteins combine with influenza virus by a specific enzymic action of the virus It is difficult to explain why in influenza the basal layer of the respiratory epithelium is not destroyed Perhaps no receptors exist in these undifferentiated cells to promote growth of the virus In this connection it should be noted that enzymes of V cholerae are capable of destroying virus receptors In experimental animals it has been found that the surface of the respiratory tract may be protected against the penetration

rhagic edematous alveolitis The septums reveal severe hyperemia hemorrhage edema and mononuclear infiltration

Detailed histologic analysis of the pathogenesis of influenza virus pneumonia in the ferret and mouse is still lacking The electron microscope studies of Eddy and Wyckoff (20) *on influenza virus pneumonia* in mice suggest that the virus destroys the alveolar epithelium and



FIG 7—Case of influenza A with bronchopneumonia in both lower lobes and right middle lobe caused by H influenzae and Pneumococcus type 3 Patient 69 died 5 days after onset of influenza A strain of influenza virus A was isolated from the trachea and lungs (concentration 10 E I D /Gm of lung tissue) (45) A section of trachea no ciliated epithelium basal cell layer is preserved distinct necrobiosis with swollen cells and nuclei (×600) B cytologic smear of trachea no ciliated cells severe degeneration with hyperchromatism of nuclear wall methylene blue stain (×200)

possibly also the endothelium of the septal capillaries At present it can only be said that the A and A′ strains are "potentially pneumotropic for ferrets and mice It is much more difficult to adapt strains of influenza B to the mouse lung

Since 1933 every case of fatal influenza virus pneumonia reported in man has been associated with pathogenic bacteria in airways and lungs Only 2 patients of Parker *et al* (58) may have shown foci of influenza virus pneumonia without bacterial superinfection

served of which 18 were superimposed on influenza virus A or B Since 1957 it has been the invariable experience in the Netherlands that occurrence of severe staphylococcal pneumonia is a sign of the presence of an influenza A or B epidemic

PATHOLOGY AND PATHOGENESIS Autopsies in cases of this type of pneumonia never reveal purulent bronchopneumonic foci solely invariably there is also a fibrinopurulent (laryngo) tracheobronchitis caused by the staphylococci The fibrin often protrudes into the lumen in the form of mushroom like clots (Fig 8A) which sometimes stain blue on section due to masses of staphylococci Large and small bronchi may become completely blocked by fibrinopurulent clots leading to atelectasis of lobes or segments Leukocytic infiltration of the walls of the small bronchioles is observed Large masses of staphylococci are found in purulent necrotic areas of the lung parenchyma

In many cases all the lobes of both lungs are involved The characteristic epithelial lesions in trachea and bronchi caused by the virus can only be identified in areas without bacterial inflammation When the latter covers the whole surface of the tracheal and bronchial mucosa the epithelial destruction can still be observed in the ducts of the tracheal or bronchial glands The obvious conjecture is that necrosis of the ciliated and goblet cells by influenza virus enables the staphylococci to gain entry into the mucosa The remaining layer of basal cells which is not affected by the influenza virus apparently does not constitute a sufficient defense against the staphylococcal infection (Figs 8B and 9) The extensive inflammatory lesion of the lung tissue may be due to mass aspiration of cocci or possibly by propagation by way of the lymphatics Only one of 18 cases personally examined revealed bacteremia (3 colonies per milliliter of blood)

A carrier of pathogenic staphylococci probably runs a risk of staphylococcal tracheobronchitis when he suffers an influenza virus infection An observation by Stokes and Wolman (73) supports this view A student nurse fell ill with influenza 3 weeks after the development of a furuncle in the left nostril and while a healing furuncle was still present on the left thigh She died 48 hours after onset of the influenza Postmortem examination revealed the characteristic picture of staphylococcal pneumonia a strain of influenza virus A was isolated A case of staphylococcal influenza A pneumonia was observed by the author in 1949 The patient was a 29 year old woman she had nursed her husband who had been ill with a staphylococcal carbuncle with septicemia The bacteriophage types of both strains of staphylococci

of influenza virus for some time after the intranasal introduction of enzymes of V cholerae

SECONDARY BACTERIAL INFECTIONS IN INFLUENZA

The frequent occurrence of bronchitis and pneumonia in influenza has long been well known The 1918 epidemic is an example of influenza with an exceptional mortality from secondary bacterial infections of lungs and airways Analysis of the relationship between influenza virus infections and bacterial involvement of lungs and airways became possible after 1933 Modern technics have confirmed that fatal cases of both influenza A and B are nearly always associated with development of secondary bacterial pneumonia Death from purely toxic causes as a consequence of influenza virus infection is unknown in man —as far as the author is aware

In a study of the interval between the onset of influenza and the appearance of secondary bacterial infections in 47 cases of virologically confirmed influenza the author could determine this interval with certainty in only 14 cases In 5 of 10 cases of staphylococcal infection the bacterial infection occurred simultaneously with the onset of influenza in the others the intervals were 3 4 5 6 and 7 days Intervals of 0 3 6 and 12 days were observed in secondary Hemophilus influenzæ infections These intervals may often be only apparent since the transition from bronchitic to pneumonic processes is often clinically difficult to ascertain

STAPHYLOCOCCUS AUREUS AS SECONDARY INVADER During the 1918 influenza epidemic the high mortality (up to 30 per cent) was in some areas caused by secondary infection with Staph aureus (15) In interepidemic cases of pneumonia the incidence of staphylococcal pneumonia is evidently much smaller than during epidemics Among 81 cases of interepidemic pneumonia Stuart Harris *et al* (79 80) found 66 cases of pneumococcal and only 2 cases of staphylococcal pneumonia In the A epidemic of 1949 however they found 51 cases of pneumococcal and 20 of staphylococcal pneumonia among 83 cases of pneumonia In many of these influenza virus A could be isolated During the 1949 influenza epidemic in Rotterdam Bruins Slot (8) observed 37 pneumonia cases 17 of which were caused by Staph aureus (among which there were 15 serologically confirmed cases of influenza A) In the period from 1946 to 1951 25 cases of Staph aureus pneumonia not associated with primary septicemia were personally ob

CLINICAL PICTURES Despite antibiotic therapy which has modified the course of this complication different clinical pictures can still be distinguished A fulminating type of the disease leads to death in toxemic shock within 24 to 72 hours of onset of the influenza In less severe infections multiple foci of purulent bronchopneumonia with or without pleural exudate or empyema may develop Unilateral processes are the exception Sometimes lung abscesses develop Temporary atelectasis of lung lobes or segments caused by fibrinopurulent bronchitis occurs at times



FIG 9 (*above*) —Case of influenza virus A with fibrinopurulent tracheobronchitis and severe purulent bronchopneumonia in all lobes of both lungs Patient 19 died 3 days after onset of the influenza Remaining layer of basal cells in the mucosa of an intralobular bronchiole Staphylococci can be seen growing on and perhaps between the flattened epithelial cells (×2 220) (Courtesy of Dr J F P Hers)

DATE 1947	2/1	2/2	2/3
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PULSE			140
ANTITITER			<12
INFL VIRUS			+

FIG 10 (*right*) —Same case as Figure 9 Course of the fulminating disease Circles temperatures taken at home dots temperatures taken in the hospital

Fulminating staphylococcal influenzal (laryngo)tracheobronchitis with bronchopneumonia Since 1941 we have observed 18 cases of bacteriologically and virologically confirmed staphylococcal influenzal pneumonia 4 of the cases were associated with influenza B Of the 18 patients 8 died all had influenza A and A Death presumably occurred on the second third (2 patients) fourth fifth eighth tenth and fourteenth day of illness and the corresponding ages were 15 19

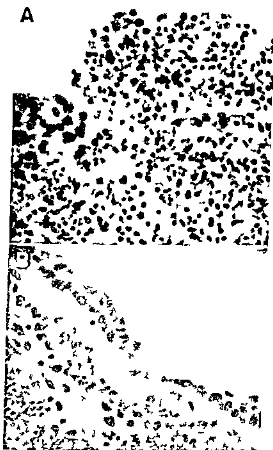


Fig 8—Same case as Figure 6 A mucosa from tracheal bifurcation Epithelial defect with protruding mushroom shaped fibrinopurulent clot Surrounding epithelium shows pathologic changes (×225) B mucosa from bifurcation Epithelium consists of one or two layers of cells only in center a defect to the right a single row of cells with round nuclei to the left a mitosis Severe hyperemia and hemorrhage in the mucosa no purulent exudate (×225)

were identical * A fulminating case (death within 3 days due to staphylococcal pneumonia) was observed in 1951 in a 19 year old girl the year before she had had severe furunculosis The frequency of staphylococcal pneumonia during the 1918 influenza epidemic may be explained by assuming that in densely populated communities both agents were spread by coughing We have not yet seen cases of contact infection with staphylococci in cases of influenza

* Dr R E O Williams Central Public Health Laboratory Collindale London

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26 40 60 34 56 and 49 years Figures 9 and 10 illustrate the case of the 19 year old patient None of the patients could be followed from the onset of the disease but the lack of antibodies in the serum of 5 of the 8 patients at death suggests that they had died within 6 days of the onset From the rapid death of some we may assume that in these patients the staphylococcal infection closely followed the influenzal infection

Patients with fulminating cases are usually admitted to the hospital in a severe toxemic state The temperature is high and cyanosis of the face may be severe although occasionally it is only slight There is moderate to severe dyspnea Cough is rarely frequent Generally there is severe retrosternal pain on coughing The sputum is very purulent *often mixed with blood* and is not abundant *Occasionally pure* blood is expectorated Both lungs reveal more or less extensive areas of inflammation in both lower and upper lobes In only 1 of our patients *was the process mainly unilateral The sputum may stain* blue (Gram s stain) due to masses of staphylococci In some cases there may be severe leukopenia (1 500 or less)

The course of nonfulminating cases depends upon the extent of the process in the respiratory tract and lungs as well as on the early or late use of antibiotics

The prognosis in influenza with a superimposed severe staphylococcal infection depends largely upon early accurate diagnosis This requires bacteriologic examination of the sputum and determination of the sensitivity of the causative strain to various antibiotics Many patients are admitted to hospital late often too late Sometimes a mistaken clinical diagnosis of diphtheria is made

Treatment When the severely ill patient does not produce sputum and a *diagnosis is suspected on clinical grounds a bacteriologic needle* biopsy of the lung is advisable The sensitivity of the infecting strain of staphylococcus to penicillin aureomycin chloramphenicol or terramycin *must be determined by rapid methods* the answer should be available within 12 hours Since penicillin insensitive staphylococcus strains may be the cause of the pneumonia aureomycin chloramphenicol or terramycin should also be given in such cases The dosages are still under study but it is believed that 4 Gm per day is necessary at first The penicillin dosages must be high (8) as the extensive necrosis in airways and lungs hampers its diffusion to the bacterial foci In all cases a minimum of *4 000 000 units of penicillin should* be given (first dose 1 000 000 units) In this way a possible superin

fection with H influenzae is also appropriately combated We have not attempted to administer penicillin intratracheally since the patients are often too ill to tolerate this procedure So far there is little evidence concerning the effectiveness of staphylococcus antitoxin Streptokinase and streptodornase may perhaps be helpful in cases with severe fibrinous tracheobronchitis Toxemic shock should be treated by augmenting the blood volume and by a short course of ACTH and cortisone therapy The autopsies on all our cases revealed more or less severe hemorrhage of the adrenal glands (41)

To date only 1 of our patients with fulminating staphylococcal infection in influenza has recovered Treatment in such cases may be extraordinarily difficult In 1 fatal case that of a 49 year old woman the causative staphylococcus strain showed a high sensitivity to penicillin After the first day in the hospital she failed to expectorate any sputum but the strain cultivated from the single colony grown from the pleural exudate (on the eleventh day) was found to be highly sensitive to penicillin Although the acute stage was overcome the patient steadily grew worse and died on the fourteenth day Autopsy *revealed the usual extensive purulent tracheitis and bronchopneumonia* in all the lobes of both lungs the pus swarming with staphylococci In contrast to the findings during life the strains isolated at autopsy proved completely insensitive to penicillin and chloramphenicol but sensitive to terramycin The bacteriophage types of the sensitive and insensitive Staph aureus strains were different All the other strains of Staph aureus found in our cases had been highly sensitive to penicillin

SECONDARY PNEUMOCOCCAL INFECTIONS Pneumococci may cause sinusitis otitis media bronchitis and pneumonia during influenza infection Pneumococcal pneumonia associated with influenza is not unusual (22 53 80)

In pneumococcal infections associated with influenza as is also the case in primary pneumococcal pneumonia the lower numerical types dominate The 8 virologically *confirmed cases observed by the author* were caused by type 1 (2 cases in one family) type 2 (1 case) type 3 (2 cases) type 5 (1 case) and type 19 (2 cases) Higher types (sometimes associated with H influenzæ) may cause bronchopneumonia At the moment secondary pneumococcal infections in influenza are among the less serious complications being amenable to treatment with antibiotics and even with sulfonamides These infections are seldom fulminating

SECONDARY HEMOLYTIC STREPTOCOCCUS INFECTIONS Hemolytic

streptococci may cause tonsillitis, sinusitis, otitis, bronchitis and bronchopneumonia in influenza. At present streptococcal bronchopneumonia is much rarer in influenza than Staph. aureus pneumonia (22, 80). In 1918 streptococcal bronchopneumonia caused a high mortality in certain areas. Except for 2 cases of Staph. aureus pneumonia concurrently associated with hemolytic streptococci, not a single clear-cut case has been seen by us in recent epidemics. Apparently the frequency of hemolytic streptococci as a pathogen has been diminishing during the past 15 years. These strains are extremely sensitive to penicillin, but the dosage must be high since this group may also cause necrotizing areas of inflammation.

TABLE I

INCIDENCE OF HEMOPHILUS INFLUENZAE IN MUCOPURULENT SPUTUM (1928-50)

CLINICAL DIAGNOSIS	CASES	H. INFLUENZAE FOUND IN SPUTUM %	H. INFLUENZAE IN ESSENTIALLY PURE CULTURE %
Acute mucopurulent tracheitis, bronchitis, bronchiolitis	315	83	48
Chronic mucopurulent bronchitis, in most cases associated with bronchiectasis (*including cases of asthmatic bronchitis*)	263	84	50

HEMOPHILUS INFLUENZAE AS SECONDARY PATHOGEN. Pfeifer (59) *discovered H. influenzae (influenza bacillus) in cases of mucopurulent* bronchitis in 1892. He associated this entirely new pathogen of the air ways with the influenza pandemic of 1889. However, the same organism was found in "ordinary" tracheo-bronchitis and bronchiolitis (65) in cases of bronchiolitis associated with measles and pertussis (48) and in cases of purulent meningitis with septicemia in infants. As a result it began to be seriously doubted whether the organism could be regarded as the causative agent in influenza epidemics. The discovery of the influenza virus in 1933 fully justified these doubts. It has now been established that even clinical observations of secondary *H. influenzae infection in viral influenza are rare*. To date not a single fatal case of secondary H. influenzæ infection in a virologically proved case of influenza has been reported. Yet there is no doubt that Hemophilus plays an important role in diseases of the bronchi and bronchioles in general. Hemophilus influenzæ suis has an essential part in the clinical picture of swine influenza in certain areas of America.

Nonencapsulated H influenzæ Quantitatively this organism is prominent in bacteriologic analyses of the sputum in cases of acute and chronic mucopurulent bronchitis and bronchiolitis (Table I) In our experience it is never found in pure culture in cases of lobar or segmental pneumonic consolidation Encapsulated type specific strains (60) are rarely observed in the mucopurulent sputum of adults in our material these were found in 7 of 439 Hemophilus strains isolated be



FIG 11 —Case of tracheobronchitis and capillary bronchitis caused by H influenzae with myocardial infarction (42) Patient 70 died of the disease No influenza virus was found in the tracheal mucosa or lung tissue There were no antibodies against influenza A B or C Tracheal mucosa showed leukocytic infiltration Note complete absence of epithelial necrosis evidence that the disease was not associated with respiratory virus disease (×300) (Reproduced by permission from J Path & Bact 63 329 1951)

tween 1946 and 1950 or about 2 per cent Patients with mucopurulent bronchitis and bronchiolitis showing a pure culture of nonencapsulated H influenzæ in the sputum can be successfully treated with antibiotics provided treatment is directed against this organism It would seem to prove that H influenzæ is a pathogen of the respiratory mucosa (56) Examination of the tracheal and bronchial epithelium in fatal cases of acute mucopurulent bronchitis and bronchiolitis due to H influenzæ has shown that the epithelial cells may be intact The conclusion to be drawn from this is that H influenzæ tracheobronchitis may occur without concomitant viral infection (41) (Fig 11) The epithelium of the bronchial mucosa also is quite normal in patients with

chronic H influenzæ bronchitis A characteristic of this organism is its ability to settle permanently in the mucosa of the nasal accessory sinuses or the bronchial tree causing chronic mucopurulent sinusitis or bronchitis generally associated with bronchiectasis This organism does not cause pneumonia The prognosis in acute cases is favorable except in acute broncho bronchiolitis Hemophilus infections are also associated with viral infections of the respiratory tract epithelium such

TABLE II

SURVEY OF 12 PATIENTS WITH INFLUENZA ASSOCIATED WITH HEMOPHILUS INFLUENZÆ OF THE BRONCHIAL TREE

ASSOCIATED DISEASE	PATIENTS	EVIDENCE OF INFLUENZA VIRUS INFECTION
Acute mucopurulent tracheobronchitis	4†	V + S (A) V + S (A) V + S (A) S (A)
Acute mucopurulent capillary bronchitis	3	V + S (A) V** (A) S (B)
Acute mucopurulent bronchitis or capillary bronchitis superimposed on chronic mucopurulent bronchitis associated with bronchiectasis	2	V + S (A) V + S (A)
Acute mucopurulent bronchitis or capillary bronchitis superimposed on asthmatic bronchitis associated with bronchiectasis	3§	V + S (A) V + S (A) S§

as measles and influenza Furthermore H pertussis promotes infection with H influenzæ

The number of cases of secondary H influenzæ infection in viral influenza that have been completely analyzed is very small Our own experience comprises only 12 cases (Table II) There are no reports of autopsies of proved cases of viral influenza associated with H influenza broncho bronchiolitis The one fatal case we have observed was also complicated by an infection with pneumococcus type 3

The coincidental infection with Hemophilus and influenza virus is easily understood Both agents are specific pathogens of the respira

V pos t e ru ol t n S h gh nt b dy t t
†On c s at d w th Ne n m n g t des n the mu opurul nt putum
On ca a so t d w th pneum o u typ 3 h w ng b n hop m n fo the l we lobe of b th lungs (d th n 3 day)
‡O e cas as c t d w th p eumoco cu typ 19
§O e case s at d w th pn umo oc typ 13

tory mucosa The necrosis of the respiratory epithelium initiated by the virus probably promotes the entry of H influenzæ into the basal cell layer and in the tissues below the basement membrane The prognosis is seldom grave provided antibiotic therapy is directed against the Hemophilus

Influenza has been observed in 5 patients with bronchiectasis (Table II) In 2 of them the presence of H influenzæ in the sputum had been established before onset of the influenza the 3 other patients were hospitalized with severe bronchitis and bronchiolitis When influenza complicates bronchiectasis the patient may become seriously ill with bacterial bronchiolitis (or bronchopneumonia) due to H influenzæ or other pre existing pathogens Hemophilus is also a common secondary invader in patients with asthma and asthmatic bronchitis (Table II) Influenza thus endangers these patients by causing an extension of the infection with H influenzæ

Treatment The first provisional diagnosis of a H influenzæ infection in viral influenza is made on the basis of Gram stains of mucopurulent sputum flakes thoroughly washed in physiologic saline Antibiotic therapy is more effective than sulfonamide treatment in such cases and should be started immediately in every case Penicillin aerosol therapy is inadvisable in my opinion high dosages are necessary (e g 5 treatments of 200 000 units per day) and results are achieved slowly Aureomycin chloramphenicol and terramycin are all satisfactory although it is not yet definitely known which is preferable Chloramphenicol 0 5 Gm every 6 hours rids the sputum of H influenzæ within 1 or 2 days but treatment should be continued for about a week to prevent relapses Resistance to this antibiotic develops rather slowly in this organism Combined penicillin–dihydrostreptomycin therapy is also very effective About 4 000 000 units of penicillin per 24 hours is the dosage necessary to control a H influenzæ infection of respiratory mucosa in adults (56) Dihydrostreptomycin alone is not recommended since 30 per cent of the strains rapidly develop resistance to this drug Benemid may economize on penicillin Jensen *et al* (47) and Heathcote and Nassau (37) reported that a penicillin e ter (benzyl penicillin β diethylamino ethylester hydriodide [Leocillin]) attains a five to tenfold concentration in lung and sputum as compared with ordinary penicillin salts In addition because of its slow absorption only two injections a day are needed

COMBINED INFECTIONS are seen in a small number of cases for example pneumococcus and H influenzæ or Staph aureus and hemo

lytic streptococcus Neisseria catarrhalis is often cultivated from the sputum associated with other microorganisms but the pathogenicity of this group is slight We have never observed it as a causative agent of bronchiolitis or pneumonia

PROPHYLAXIS OF SECONDARY BACTERIAL INFECTIONS The sulfonamides are prophylactic against the pneumococci and hemolytic streptococci but probably not against Staph aureus and H influenzæ The harmful or disagreeable side effects of these drugs are also a considerable disadvantage Procaine penicillin in ordinary dosage will usually prevent pneumococcal and hemolytic streptococcus infections possibly also infections of sensitive Staph aureus This dosage is ineffective against H influenza infection Aureomycin chloramphenicol and terramycin 2 Gm per day have a broad prophylactic value against respiratory pathogens (including H influenzæ) Prophylaxis with antibiotics is important in the following situations (*1*) If a patient with influenza has or is known to have had furunculosis infected skin injuries or infected eczema (*2*) In families or communities where furunculosis or bacterial influenzal pneumonia is present (*3*) In diabetes (*4*) In pregnant women (*5*) In persons over 50 years of age (*6*) In persons with chronic sinusitis secondary infected asthmatic bronchitis and chronic mucopurulent bronchitis (bronchiectasis) All these patients should receive daily chloramphenicol aureomycin or terramycin to prevent a possible extension of H influenzæ infection

MOBILIZATION AFTER UNCOMPLICATED VIRAL INFLUENZA The return to normal occupation after influenza should not be too rapid Regeneration of the epithelium takes from 8 to 10 days and it is not completely normal until 3 to 4 weeks after the illness The patient should remain at home for at least 1 week after the fever has subsided

VACCINATION AGAINST INFLUENZA

The investigations of Francis *et al* have revealed many facts with regard to anti influenza vaccination But the subject is so complex that many questions are still unanswered

An influenza virus infection of the respiratory tract causes a moderate to very high production of antibodies in the blood of man or experimental animals Determinations of the circulating antibody titer during interepidemic intervals have shown that the figures vary greatly With the hemagglutination inhibition test they may range from about 1 30 to 1 1 000 though high values are exceptional (67) The mei

dence of influenza is lower in persons with a pre existing high antibody titer than in persons with a low titer (63 67)

It is practically certain that the natural disease provokes an immunity of at least 8 weeks duration no cases of two distinct infections caused by the same serologic type of influenza virus during the same epidemic have been reported How long this natural immunity lasts is not definitely known for only rarely have patients been observed who have twice contracted influenza due to the same serologic type of influenza virus The periodic recurrence (about every 2 years) of influenza A and A′ seems to indicate that in the community as a whole there is a fairly long postepidemic immunity This view is supported by the titers of the circulating antibodies found after and between epidemics

Experimental Vaccination Vaccination has been studied in ferrets and mice since the discovery of the influenza virus in 1933 The existence in mice of a positive correlation between the quantity of immunizing virus and the degree of protection against subsequent intranasal infection has been proved (21) The immunity obtained is proportional to the quantity of circulating antibodies However the protection provided by circulating antibodies is only indirect it is the quantity of antibodies appearing on the surface of the respiratory tract after vaccination that directly determines the degree of immunity This is clearly demonstrated by intranasal vaccination with formalinized virus which provokes a comparatively low titer of circulating antibodies but a high concentration in the respiratory tract A far greater degree of protection is obtained by this technic than by intraperitoneal or subcutaneous vaccination After the latter the quantity of circulating antibodies is high but only a little appears on the surface of the bronchial tree Intranasal vaccination with live influenza virus provides the strongest protection against subsequent intranasally induced influenza (21)

Vaccination in Man Cultivation of the influenza virus in chick embryo has led to rapid development of new technics for preparing large quantities of concentrated influenza virus (72) Subcutaneous vaccination with formalinized human influenza virus results in a varying rise in antibody titer in the blood depending upon the concentration of the virus in the vaccine (26 39) About 20 per cent of those vaccinated show no rise in antibody titer or a very slight one The rise is most marked in persons with low prevaccination titers As a rule no rise is observed when the prevaccination titer is high Revaccina

tion shortly after the first inoculation therefore has little or no effect The antibody titer starts to rise on the fifth or sixth postvaccination day and the maximum value is attained after about 2 weeks (Fig 12)

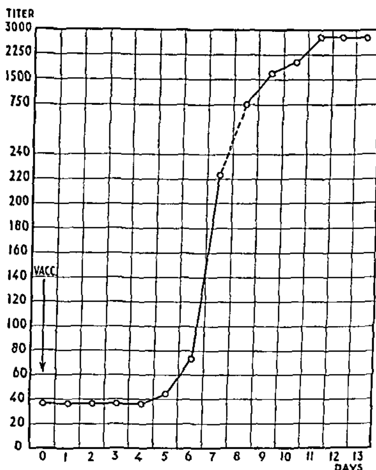


FIG 12—Effect of subcutaneous vaccination with 1 ml of concentrated A (FM1) vaccine (CCA titer 15 000 0 125 per cent final red cell concentration) on antibody titer in serum Note beginning of the rise on the fifth day with maximal level on eleventh day

The titer then drops but as long as a year after vaccination it may still be higher than the prevaccination level (45 68) Comparison of the titers produced by vaccination in man with those in experimental animals shows that the former are generally higher although mice and ferrets receive comparatively much larger doses of vaccine Vaccina

tion of human beings (if not too young) even with relatively small quantities of antigen will probably stimulate the production of anamnestic immune bodies resulting from previous experience with the virus

Intracutaneous vaccination with 0 1 ml of vaccine causes fewer local and systemic reactions than subcutaneous inoculation with a tenfold quantity This method provokes a highly satisfactory rise in serum antibodies (9) Intranasal vaccination (by aerosol or instillation) with influenza virus (live or dead) has been advocated on theoretic grounds especially by Burnet This method however has been less exhaustively investigated than the parenteral route Live virus (virulent for mice) administered intranasally often causes an influenza like disease attended with a rise of serum antibodies (32 40) Live egg virus with attenuated virulence may be inhaled without causing systemic reactions but does not provoke a high rise in serum antibodies (12) Quilligan and Francis (61) vaccinated groups of children by means of intranasal aerosol with highly concentrated formalinized vaccine and observed a marked increase of serum antibodies Intranasal vaccination of man has not been studied with respect to the production of antibodies on the surface of the respiratory tract

Burnet *et al* (14) and Francis (24) observed that nasal secretions of human beings may contain neutralizing antibodies against influenza virus The titer of this antibody is low and it rises after natural infection (28) but also after subcutaneous vaccination (30) It seems certain therefore that these respiratory antibodies are identical with those in the blood serum The titer of the antibodies in the respiratory tract—more important than the antibodies of the blood serum—have been studied only on a small scale Determinations in 20 vaccinated volunteers by means of the hemagglutination inhibition test have been made (54) the nonspecific inhibition of the nasal secretion being neutralized with enzymes of V cholerae In 16 of the 20 vaccinated persons a satisfactory titer developed in the nasal secretions after intracutaneous vaccination with concentrated monovalent vaccine the titer of the nasal secretion rising on an average to 3 per cent of the blood titer

These experimental data indicate that a moderate to high rise in titer of circulating antibodies can be effected in man after a parenteral injection of formalinized virus and that after vaccination antibodies make their appearance on the nasal mucosa

The first large scale experiments with volunteers were performed

by Francis *et al* (32) These workers vaccinated 66 persons with a commercial vaccine (concentrated virus from the allantoic fluid of chick embryos containing 50 per cent influenza virus A and 50 per cent influenza virus B) A control group consisted of 36 adults Both groups were intranasally inoculated with an influenza A strain (isolated a short time previously and virulent for mice) belonging to the same serologic type as the A strain in the vaccine (A PR8) In the control group 50 per cent became ill with temperatures of 100 F and over (highest temperature was 103 F) and general symptoms of influenza with an incubation period of 24 to 48 hours Of the 38 persons who were intranasally inoculated 2 weeks after subcutaneous vaccination clinical signs developed in only 15 per cent and none showed a temperature over 100 F Of 20 persons who had been vaccinated 4½ months previously 30 per cent became ill after injection Postvaccinal induced infection with a strain of influenza B caused illness in 10 per cent of the experimental persons as against 40 per cent of a control group

In 1943 6 200 persons in 6 widely separated study groups were inoculated with a commercial vaccine consisting of a mixture of two influenza A strains (18 19 23 36 45 52 64 67) The same number of persons serving as controls did not receive influenza virus Vaccinated and control persons stayed in the same buildings Circumstances favored the experiment for a short time after vaccination (November 1943) there was an outbreak of a fairly extensive influenza A epidemic The incidence of patients hospitalized with fever was 2 2 per cent in the vaccinated and 7 1 per cent in the control group One of the 6 centers (19) showed no favorable results—5 2 per cent influenza in the vaccinated and 7 8 per cent in the nonvaccinated group

In this experiment Hirst *et al* (46) and Hale and McKee (36) made interesting observations when the influenza epidemic broke out among recently vaccinated groups During the 7 days following vaccination the number of patients in the vaccinated group was about equal to that in the control group but thereafter the number of cases in the vaccinated group diminished considerably

The personnel of the U S Army was vaccinated against influenza in October 1945 with a mixed vaccine of influenza A and B In the early part of November 1945 influenza appeared and studies were made in separated groups In two vaccinated groups the morbidity was reduced by 90 and 96 per cent respectively as compared with nonvaccinated units

The American mass experiment proved that the vaccine is perfectly harmless Care should be exercised in persons with allergy to chicken protein since influenza vaccines will contain traces of it No postvaccinal encephalitis occurred but this may not hold true for all countries Encephalitis after other types of vaccination is also rare in the United States

A third vaccination experiment in March 1947 did not yield results comparable to those of the 1943 study (33) The causative virus strain (A) in this epidemic was antigenically different from the strain (A PR8) found in earlier epidemics Recently Meiklejohn *et al* (53a) using a monovalent vaccine against the strain A FM_1 found a clear cut reduction in incidence of influenza in the vaccinated unit

Vaccination against influenza will evidently reduce the incidence of infection provided the strain (or strains) used in the vaccine corresponds serologically to the virus causing the epidemic

Certain questions concerning the problem of anti influenza vaccination remain unanswered Respiratory antibodies play a decisive part in the defense against influenza in combination with cellular immunity in the respiratory tract and the lungs Cellular immunity cannot be raised artificially Thus the titer of the respiratory antibodies should probably be raised by increasing the titer in the blood serum as high as possible At present one is satisfied when the antibody titer in the blood rises to about 500 after vaccination It rarely rises to 12 000 or higher In experimental animals it is not difficult to provoke a very high titer of the circulating antibodies by using certain adjuvants (34) Henle *et al* (38) used adjuvants for the subcutaneous vaccination of human subjects against influenza Skin abscesses developed in a small percentage of the cases

Salk *et al* (66) continuing the work of Friedewald made use of an adjuvant consisting of a light mineral oil (Bayol F) with an emulsifying agent (Arlacel A) and avoided undesirable local reactions by giving the vaccine intramuscularly Very high and long standing titers were consistently obtained in monkeys The effect in men is now under study

If highly concentrated vaccine is used the vaccination must be done intracutaneously to avoid the systemic reactions which may be caused by subcutaneous injection of highly concentrated material

Effect on Influenza Virus Pneumonia Smith *et al* (71) demonstrated that for some time after subcutaneous vaccination with live virulent influenza virus ferrets were not always completely immune to

the homologous virus and that an infection of the nasal mucosa could still develop However influenza virus pneumonia did not develop when the immunized animals were infected with a pneumotropic ferret strain of the virus Why vaccination should protect lung tissue better than the respiratory tract epithelium is not clear The histologic structure of the epithelium in nose trachea bronchi and bronchioles differs widely from that of the lung alveoli Perhaps the contact between the circulating antibodies and the susceptible cells is more easily established in the wall of the alveolus than in the epithelium of the respiratory tract Far more study is required to clear up this important but obscure problem

OTHER ASPECTS OF VACCINATION PROBLEM The differences in antigenicity of the many influenza virus strains make it difficult to prepare an effective vaccine It cannot be predicted with certainty which serologic type will cause the next epidemic It is probable that the next period will be dominated by the subgroup A′ The antigenic effect of A vaccines is undoubtedly less than that of PR 8 vaccines (3) so that high concentrations of the former seem advisable

Subcutaneous vaccination insures reasonably high antibody titers in the blood for a few months only It follows that vaccination is a wise measure when an epidemic is impending In this connection it should b remembered that influenza A (A′) appears on the average every other year in the Northern Hemisphere nearly always between November and March

A polyvalent vaccine contains a lower concentration of the constituent virus strains than a monovalent vaccine Thus the former will generally produce a smaller increase of antibody titer than a monovalent vaccine Vaccination with a monovalent vaccine would therefore be preferable the various strain types being injected in turn However this method is cumbersome and expensive in practice so that usually polyvalent vaccines adapted to the prevalent strain types are used In our opinion the old PR 8 type should be omitted and the B Lee strain (isolated in 1940 by Francis) be replaced by a more recently isolated representative of the B group

Whether vaccination should be done subcutaneously or intracutaneously is an important question We vaccinate adults intracutaneously using 0 3 ml of a highly concentrated monovalent vaccine This is done in order to avoid side reactions as much as possible and for reasons of economy The antibody titers produced by this dosage of vaccine are at least equal to those obtained with a subcutaneous

administration of a threefold quantity The use of adjuvants (66) may in the future completely change the technic of anti influenza vaccination

At present it seems inconceivable that sufficient vaccine could be produced to vaccinate a population running into millions To attain a reasonable distribution of protection for healthy individuals vaccination must be selective Priority should be given to physicians and nurses and to patients with chronic sinusitis bronchiectasis bronchial asthma and tuberculosis since in these a severe bacterial superinfection may develop Vaccination is also advisable for known or suspected carriers of pathogenic staphylococci for patients with diabetes and for pregnant women

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Experiences with Adrenocortico-tropic Hormone (ACTH) and Cortisone*

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IN 1949 Hench *et al* (14 15 16) announced that the symptoms of rheumatoid arthritis rheumatic fever and lupus erythematosus disseminatus were ameliorated by the administration of cortisone or ACTH With the intervening period of experience as a background a preliminary evaluation of the therapeutic effectiveness of these hormones seems reasonable

In this group of diseases there is first no obvious insufficiency of adrenal or pituitary function insofar as known functions involving electrolytes carbohydrate nitrogen and gonads are concerned and second nothing is known concerning their pathogenesis The group name—diseases of the connective tissue—is used since loose undifferentiated connective tissue and blood vessel walls are involved in an inflammatory process of unknown etiology

Some degree of hyperadrenalism is necessary to modify the symptoms of these diseases beneficially for the patient Moderate hyperadrenalism modifies the host reaction to all types of inflammation studied so far Induced hyperadrenalism leads to (*a*) a delay in the

*Supported in part by a grant from the Masonic Foundation for Medical Research and Human Welfare and the United States Public Health Service

reaction of connective tissue to trauma (24) (*b*) a delay in repair processes (6 23) (*c*) a delayed appearance and a decrease in the number of white cells (polymorphonuclear leukocytes and macrophages) invading an area (9) (*d*) an inhibition of the phenomenon known as margination of white cells (11) and (*e*) a decrease in capillary permeability (5) Little is known concerning the initiation of the inflammatory response but some substance is probably elaborated at the site of trauma be it infectious or mechanical which starts the train of the inflammatory reaction Presumably the elaboration of this substance is inhibited locally by the action of cortisone or cortisone like steroids secreted by the adrenal cortex during hyperadrenalism Although cortisone (or ACTH through stimulation of an endogenous output of cortisone like substances) will modify the inflammatory reaction of rheumatoid arthritis and allied diseases one must keep in mind that all types of inflammation as well, will be modified. This change in the reaction of the host leads to many of the untoward reactions seen during administration of cortisone or ACTH

RHEUMATOID ARTHRITIS

Nothing is known concerning the pathogenesis of rheumatoid arthritis Its natural course is varied and to the best of our knowledge completely unpredictable During hyperadrenalism induced by the administration of cortisone ACTH or Compound F the symptoms and signs commonly associated with this disease are without question modified beneficially for the patient Stiffness after inactivity, joint pain, redness and swelling early flexion contractures fever, tachycardia, elevated sedimentation rate and hyperglobulinemia disappear or subside

During several months of treatment of rheumatoid arthritis with cortisone or ACTH no significant decrease was observed in the amount of circulating antibody to group A hemolytic streptococci or to the sensitized sheep cell agglutination This led to the belief that these serologic reactions were perhaps manifestations of the underlying disease process rather than the response of the host to the disease such as is the sedimentation rate and hyperglobulinemia However as our experience with the sustained hormonal remission becomes more protracted patients are appearing in whom these serologic reactions are becoming weaker In certain instances—6 of 36 patients—this weakening of the antibody to group A hemolytic streptococci has been signifi

cent Certainly the reversal of the reaction is a much slower process than the return to normal of other protein changes

In the great majority of instances the beneficial response to hormone administration persists only until or for a short time after the hormone is discontinued and then symptoms recur In the experience of some workers notably that of Freyberg (12) remissions have been sustained following withdrawal of hormone in 14 per cent of instances In our group of patients this sustained remission following withdrawal accounts for less than 5 per cent Hormone has been withdrawn in 21 patients after 4 to 6 months of administration only 1 patient has sustained a partial remission for more than 2 months after withdrawal The variation in remission rate after withdrawal can be attributed to the variable nature of the disease if treatment is instituted during a period of improvement a sustained remission may be expected if the curve of activity has subsided before the hormone is withdrawn

Following withdrawal there is a phenomenon known as the "rebound" in which the activity of the disease may be more severe than before therapy was instituted in certain instances fever and sedimentation rate may be higher than in the pretreatment period This may or may not represent a true increase in activity but there is no doubt that frequently there is an increase in symptoms during this period It has been suggested that patients may lose their acclimatization to the disease during hormone administration when they are free of pain and thus be able to tolerate symptoms less well when these return

A depression of adrenal function is to be expected with cortisone administration The adrenals normally are stimulated by the pituitary which in turn is stimulated by a drop in level of circulating cortisone like substances When such substances are administered by the exogenous route the pituitary is not fired and the adrenal in the absence of endogenous ACTH atrophies to a varying degree Overt adrenal insufficiency manifested by a low serum sodium or hypoglycemia is rarely found upon withdrawal of cortisone During this period in which the adrenal fails to respond to a test dose of ACTH by a fall in eosinophils the patient reacts poorly to stress and traumatic episodes which would ordinarily be of little concern may assume major importance

Since a return of symptoms following withdrawal of hormone may be expected in the large percentage of patients interval hormonal treatment is rarely if it all effective and in the majority of instances one must resort to a course of sustained induced hyperadrenalism It

is generally accepted that the induction of a minimal amount of hyper adrenalism will most readily achieve some beneficial effect The longer an induced hyperadrenalism is sustained the more difficulties may be expected The beneficial effects on the disease must be balanced against the problems which will arise and the evaluation of this balance is always a calculated risk

The problems to be anticipated can be classified under several headings (1) Suppression of the inflammatory reaction (2) difficulties related to the known functions of the adrenal and (3) difficulties of which the mechanisms are not understood

SUPPRESSION OF INFLAMMATORY REACTION The ordinary individual during the course of his life sustains many mechanical and infectious traumatic episodes The usual euadrenal organism is able to cope with these quite adequately but in the presence of hyperadrenalism such minor injuries assume a major importance Many of the symptoms of the inflammatory reaction and the diagnostic signs associated with it are modified during induced hyperadrenalism A hyperadrenal patient may develop an acute abdominal condition following perforation of a viscus with relatively little abdominal pain no rebound tenderness and no localizing signs If pneumonia sets in physical findings in the chest may be modified fever absent and an inflammatory reaction poorly localized Such poor localization is notable in the abscesses which follow incomplete asepsis in injecting the hormone in pneumonia occurring during induced hyperadrenalism which can spread rather widely in tuberculous lesions which in the pretreatment period have been well controlled but become overt with a positive sputum during hormonal administration In viral infections like poliomyelitis and vaccinia it has been shown in animals that viruses are more virulent and spread more widely during hyperadrenalism

DIFFICULTIES RELATED TO KNOWN ADRENAL FUNCTIONS During hyperadrenalism patients are prone to retain salt and water which may lead to edema and congestive failure In sustained therapy some sodium restriction is usually necessary The hypertensive reaction in our experience seen with both cortisone and ACTH may possibly be associated with sodium retention A decreased tolerance to carbohydrate may be observed but rarely does this reach diabetic proportions and ketosis is rare with this intolerance to carbohydrate Insulin treatment of the diabetes leads to a therapeutic regimen which is difficult to maintain and under such circumstances continuation of cortisone or ACTH therapy is rarely warranted A negative nitrogen balance is

commonly associated with even therapeutic doses of cortisone or ACTH but the significance of this to the patient may be negligible Osteoporosis is to be expected from the natural course of Cushing's syndrome but a measurable increase in demineralization has so far not been observed with cortisone or ACTH therapy In rare instances muscle weakness due to low tissue potassium may be seen This is usually associated with large doses of hormone or with the use of mercurial diuretics since potassium is excreted with sodium and water following mercury induced diuresis Generally hypokalemia is not a major problem in the routine use of these hormones However when diuretics are used or when large doses of hormone are required careful supervision of the potassium level is necessary If this is not feasible because of the lack of a flame photometer in the laboratory daily administration of 2 to 4 Gm of enteric coated potassium chloride will usually cover any eventuality

Difficulties of Which Mechanisms Are not Understood The third group of potential difficulties which may be expected during administration of these hormones is of unknown etiology although there are some theories concerning the initiation of each Ordinarily a patient with rheumatoid arthritis receiving cortisone or ACTH experiences a certain degree of well being attendant upon the decrease in pain and stiffness and increase in ability to enjoy life However occasionally this progresses in a somewhat stepwise fashion to an excessive sense of well being which may develop into mania It is noteworthy that in our experience at least true mania has been seen only in patients with rheumatoid arthritis and asthma In other diseases the reaction may be of a schizophrenic type with a catatonic or a paranoid pattern Associated with the use of these hormones certain abnormal electroencephalographic patterns are seen (17) and thalamic and hypothalamic lesions have been noted in rats given large amounts of cortisone (7) These two findings may indicate that the psychotic episodes have an organic basis The pathogenesis of these mental reactions has not been established although the frequency with which *they are seen in naturally occurring Cushing's syndrome* favors the thesis that the hyperadrenal state is the cause of the reaction Clinically these abnormal mental reactions subside after a shorter or longer period following cessation of the hormone therapy Specific therapy may be required in mania since the patient may overreact during the manic phase to the point of self damage Shock therapy is indicated in such cases In our experience the patient resumes his normal mental pattern after 3 or 4 treatments

Evidence has been presented suggesting that cortisone or ACTH therapy is followed by the *de novo* development of a peptic ulcer this may be troublesome since the usual symptoms of a peptic ulcer tend to be masked during hormonal administration The increased urinary excretion of uropepsin after administration of ACTH or cortisone (13) is possibly related to the suggested increased incidence but in such a common syndrome it is difficult to be certain of a true cause and effect relationship In 2 of our patients a new peptic ulcer developed during the treatment with cortisone or ACTH Of 3 patients with a known peptic ulcer before the administration of cortisone or ACTH only 1 has had a temporary increase in ulcer symptoms during hormone therapy Some feel that the presence of a peptic ulcer is a contraindication to the use of ACTH or cortisone but as in all such contraindications the beneficial effects to be expected from the therapy must be weighed against the possible untoward effects associated with it The administration of these hormones must always be considered a calculated risk

A third symptom complex of unknown pathogenesis is the development of thromboembolic phenomena In a large series of patients treated with ACTH or cortisone the incidence of such complications has been found to be about 3 per cent (25) There are no adequate data at this time concerning the occurrence of such thromboembolic phenomena in a similar group of patients not treated with hormone In our group of patients with rheumatoid arthritis treated with hormones on a sustained program cerebral accidents occurred in 2 patients 1 of whom died 3 patients had had thrombophlebitis in the past and 2 of these experienced second episodes during hyperadrenalism 1 with a subsequent pulmonary infarct In a fourth patient pulmonary infarcts also developed during the withdrawal period but there had been a similar episode in the distant past Such thromboembolic phenomena may appear during the hormone therapy or following withdrawal Cosgriff *et al* (8) have noted an increased coagulability of the blood during hormone administration which persists for several weeks after withdrawal This has led some to feel that cessation of therapy should not be undertaken lightly

Certain unpleasant but insignificant phenomena may be expected to develop during hormone administration Among these are Cushing's facies acne hirsutism and obesity associated with a voracious appetite Cushing's facies may be a nuisance to the vanity of the patient but indicates only that hyperadrenalism has been induced with all that that implies Acne has not been troublesome with the dosages of hormone required to control partially the symptoms of rheumatoid

arthritis Hirsutism is a problem in young women but if the patient complains of hirsutism the indications for the induction of hyper adrenalism have probably not been sufficient to warrant the risk since a slight amount of hair on the face when bleached adequately is of minor importance when compared with invalidism Our patients are advised to ignore it Hirsutism will disappear when the hormone is withdrawn and the patient must choose between it and arthritic symptoms Obesity associated with an increased appetite can pose quite a problem These patients regularly gain weight even with salt restriction and the increase in weight may be very great It represents one of the most annoying problems faced during long continued hyperadrenalism The tendency may be controlled with rigid restriction of food intake but it is difficult because of the excessive appetites which these patients develop

All such unpleasant and undesired reactions to hyperadrenalism subside when the hormone is withdrawn Our first principle of treatment has been to withdraw the hormone whenever we were concerned about the patient With accumulating experience we tend to be less cautious and continue therapy through certain crises At present we feel strongly that the hormone should be discontinued in the following circumstances (1) when a psychosis develops (2) when an inflammatory process develops such as an injection abscess a possible tuberculous lesion or a pneumonia (3) when there is a possibility that an intraperitoneal catastrophe has taken place (4) when there is evidence of thromboembolism We have tried—so far successfully—to maintain the hyperadrenal state in the presence of a peptic ulcer mild diabetes hypertension mild infection during orthopedic surgery sodium retention and mild congestive failure and in hypokalhemia Whether this is wise or not we cannot now say But since most patients with rheumatoid arthritis do so badly when hormone is withdrawn we feel that every effort should be made to continue it and withdrawal ideally should be carried out with the hope that a spontaneous remission will follow However our first principle of treatment continues to be cessation of the hormone when we are concerned about the patient or when an explanation for a symptom or sign is not readily forthcoming

Certain safeguards in using cortisone or ACTH must be considered and should be used in sustained treatment with these hormones Perhaps the most important is that the patient be kept under frequent and careful supervision If this is done most of the major difficulties can

be minimized or avoided Weight should be checked frequently and sodium and water retention guarded against by sodium restriction if necessary The blood-pressure should be followed daily at the start and weekly or biweekly thereafter If possible the serum potassium level should be followed as well If this is not possible the use of enteric coated potassium chloride in a dosage of 2 to 4 Gm a day will control most of the troubles associated with hypokaliemia Of extreme importance in this careful supervision is that minimal signs and symptoms of a marked inflammatory process be inquired for and if present be carefully evaluated During cortisone or ACTH administration a slight rise in white blood cells may be expected chiefly in the polymorphonuclear leukocytes for this reason the white blood cell count is of relatively little value in the careful control of these patients If the development of masked signs or symptoms causes concern the hormone must be stopped and the patient observed carefully since following the withdrawal of cortisone particularly the patient is in latent adrenal insufficiency and responds poorly to stress when compared to the normal individual

Choice of Hormone and Route of Administration

Cortisone or ACTH may be chosen as well as the route of administration of each Cortisone given intramuscularly has a slow but long lasting action and many patients may be maintained with 3 injections a week However with the danger of poor localization of inflammation the most rigid asepsis is required to prevent the development of abscesses In general these patients cannot carry out such asepsis themselves and frequent visits to the doctor s office or the clinic are necessary The other disadvantage of intramuscular administration of cortisone is that during emergencies when hormone should be withdrawn rapidly withdrawal is of necessity slow since the hormonal effects may last for 3 or 4 days following the last injection

Cortisone orally acts quickly and when withdrawn loses action quickly It must be given frequently during the day—3 4 or 5 times—and occasionally in patients with severe disease is not effective since during the night a symptomatic escape will take place Slightly more hormone is needed per week with oral use as compared with intramuscular administration The oral route is far easier for both patient and physician and therein lies danger since it is almost too easy to use In several observed instances patients who were taking cortisone

by mouth without medical supervision did not require the hormone while serious difficulties developed in others

Aqueous ACTH must be given 2 or 3 times a day intramuscularly, oral administration having proved a complete failure. There is a *slightly greater increase in blood pressure with ACTH than with cortisone* and somewhat greater salt and water retention; however, our patients on ACTH have done well and a smooth control of the disease has been effected. Since 2 or 3 injections a day are necessary, patients must administer the hormone to themselves and the danger of injection abscesses is greater. A number of clinical reports have appeared concerning ACTH rendered long acting by combination with various menstruums. In our experience—short lived to date—with long acting ACTH in gelatin given every 2 days, control of the disease has been eminently satisfactory.

Compound F, or the analogue of cortisone with a hydroxyl group in the 11 position rather than an oxygen atom, acts essentially like cortisone when given intramuscularly or orally. Hollander *et al* (18) have *recently reported that Compound F given intra-articularly* has a beneficial effect upon the symptoms of the rheumatoid joint, whereas cortisone thus given has not. This has been confirmed insofar as the local articular effect is concerned. The observation is somewhat surprising since cortisone locally has an anti-inflammatory (10) and antirepair (1) action on connective tissue. To the best of our knowledge Compound F offers no more than cortisone when given either intramuscularly or orally to the patient with rheumatoid arthritis.

Dosage Schedules

During sustained treatment, since one must expect to continue the administration of hormones for long periods of time, a plan should be followed whereby the lowest possible amount of hormones is administered which is related to a beneficial effect. The amount needed to produce such a suboptimal remission varies with each patient, with the severity of the disease and with the amount of extraneous stimuli such as worry or physical exertion which in turn may influence the severity of the disease. In certain instances it has been reported that 50 mg of cortisone daily by mouth in divided doses will sustain an adequate remission. Our group of patients need between 75 and 150 mg a day to maintain a beneficial effect and smaller doses than this are without effect. However, these are patients with severe rheumatoid arthritis of clinic status and have been chosen particularly be

cause they have severe disease The average case of severe rheumatoid arthritis can be partially controlled to the point of social and economic self sufficiency by cortisone given intramuscularly Monday Wednesday and Friday in a dose of 200 100 and 200 mg respectively or by 100 to 125 mg of cortisone a day by mouth in divided doses before meals and at bedtime or by 40 mg of ACTH in divided doses 2 or 3 times a day We have had 2 patients whose severe rheumatoid arthritis could not be adequately controlled with 150 mg of cortisone daily by mouth now in fair control with 100 to 125 mg daily given intramuscularly These dosages are hazardous and should not be considered unless the patients are under very close supervision and unless control of the patient s arthritis warrants such amounts Dosages of 100 100 and 200 mg cortisone intramuscularly on Monday Wednesday and Friday or 75 to 100 mg a day by mouth or 40 mg of ACTH a day in 2 or 3 doses can be considered fairly safe As stated above the amount of hormone required varies with the severity of the disease when the patient is under great tension or is subjected to excessive physical exertion more cortisone or greater restriction of activity may be needed

Recently Bayles *et al* (3) have suggested the technic of massive dose administration for a short time leading to a remission sustained for a greater or longer period It is noteworthy that in these authors opinion the amount of cortisone needed to control a patient is similar whether it be given daily 3 times a week or for 3 weeks out of a 2 month period In this massive dose technic untoward effects are potentially of major magnitude and the hormone must be given under careful hospital supervision This regimen may prove to be of value and needs further study

Logically the hormone should be withdrawn at certain intervals in an effort to see if a spontaneous remission will ensue but it must be remembered that there are certain hazards to hormone withdrawal In the first place experience has shown that during withdrawal there is an increased incidence of thromboembolic phenomena In our own experience there have been 2 such episodes of thromboembolism during withdrawal A second hazard is that of latent adrenal insufficiency following cessation of cortisone administration It has been suggested that this may be overcome by the administration of ACTH concomitantly with cortisone for a week prior to withdrawal with both stopped simultaneously This regimen of withdrawal needs further evaluation

The value of salicylates with cortisone has not been resolved Cer

tainly the concomitant use of salicylates will materially decrease the amount of cortisone or ACTH necessary to control the disease However the increased gastrointestinal irritation induced by salicylates may represent a hazard in those patients whose symptoms are difficult to interpret during hyperadrenalism

It is extremely important that the commonly accepted therapeutic adjuncts be continued when a patient with rheumatoid arthritis is receiving hormone These include active exercises and the usual measures of physical medicine The patient receiving hormone may continue active exercises beyond pain and fatigue limits without subsequent increase in symptoms and it is in this field that one of the greatest advantages of these hormones may be anticipated Furthermore procedures of orthopedic surgery can be carried out while a patient is on cortisone At the usual therapeutic dosage incised wounds will heal adequately if the sutures are left in place for a longer time than usual However we have been somewhat discouraged in recent months with our efforts to rehabilitate patients with severe damage due to rheumatoid arthritis who require all the measures of physical medicine and all the measures of orthopedic management both operative and non operative to regain an adequate social and economic existence This has called for a major output on our part with minimal benefit to the patient It remains to be seen whether such a large out

TABLE I

SUMMARY OF 59 PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH SUSTAINED INDUCED HYPERADRENALISM FOR 3 TO 26 MONTHS (MEAN 9 MONTHS)

Duration of disease				1–70 years
Sex				male 23 female 36
Age				13–78 years
Steinbrocker classification (27)				
Grade 1	0	Class I	0	
Grade 2	13	Class II	22	
Grade 3	29	Class III	23	
Grade 4	17	Class IV	14	
Treatment				
Oral cortisone alone				5 patients
ACTH alone				11 patients
Intramuscular cortisone alone				31 patients
Daily			2	
2 to 3 times a week			22	
Once a week			7	
Various combinations of oral or intramuscular cortisone and ACTH				12 patients

lay of time and money is justified when it produces such minimal benefit

Tables I, II and III summarize our experience with ACTH and cortisone therapy in rheumatoid arthritis

Aim of Therapy

The aim of treatment of rheumatoid arthritis should be the return of the patient to a normal life Salicylates have been used for many years in the treatment of rheumatoid arthritis to increase the patient's comfort and thereby permit an increase in physical activity The use of cortisone and ACTH seems to be developing along similar lines at

TABLE II

Change in Work Capacity during Sustained Hyperadrenalism

Status	No. of Patients Pretreatment	No. of Patients During Treatment
Bedridden	10	4
No work	21	3
Part time work	14	21
Full time work	4	31
Using canes or crutches	33	12

Major flexion contractures persist despite exercises in addition to hormone in 5 patients

Arthroplasty for correction of flexion contracture performed in 2 patients †

New flexion contractures have developed of minor degree in 2 patients

Two of these [illegible] period [illegible] 3 and 4 months [illegible] part time [illegible] full time work but [illegible] bedridden

Two died.

† [illegible] bedridden after 12 [illegible] 9 months [illegible] hormone [illegible] and 5 to 6 months [illegible] arthroplasty

least in our experience We have been able to increase the comfort of our patients greatly but whether our aim—the return to a normal existence—has been achieved is uncertain Certainly a large number of our patients who worked part time or not at all have become economically self sufficient to some extent However 2 of 10 bedridden patients with severe disease who were able to resume their occupations have with the passage of time returned to a bedridden existence although still receiving hormone These 2 patients could not be maintained on a plane of satisfactory economic and social existence

What then can be accomplished by the use of these hormones in rheumatoid arthritis? In the first place the patient with mild rheumatoid arthritis can be maintained with minimal amounts of hormone although before the era of cortisone and ACTH many such patients were also adequately controlled It is questionable whether or not ad

TABLE III

COMPLICATIONS ENCOUNTERED DURING SUSTAINED INDUCED HYPERADRENALISM

Age Yr	Hormone Therapy Mo	Necessitating Permanent Cessation of Hormone Administration
48	8	Thrombophlebitis with pulmonary infarction
49	9	Bronchiectasis with overwhelming pulmonary infection and death
78	6	*Dizziness blurring of vision mental confusion*
55	7	Pulmonary tuberculosis with positive sputum
42	5	Suicidal attempt with barbiturates (manic-depressive psychosis necessitating shock therapy after short course of ACTH previously)
72	6	*Cerebrovascular accident and death*
73	9	Congestive failure pneumonia pulmonary infarction
38	3	*Improvement not worth the trouble*
56	4	Improvement not worth the trouble
		Necessitating Temporary Cessation of Hormone Administration
51	16	Marked carbohydrate intolerance with furunculosis and peripheral neuritis
63	10	Diverticular abscess with perforation and sinus tract formation requiring drainage and permanent colostomy pulmonary infarction postoperatively
55	17	Cerebrovascular accident with recovery
		Pneumonia in 5 patients
46	9	Acute cholecystitis and common duct obstruction requiring cholecystectomy and duct exploration
		Not Requiring Cessation of Hormone Administration
69	7	Carcinoma of parotid with facial palsy requiring biopsy and radiotherapy
41	14	New duodenal ulcer symptomatically controlled with salicylate reduction and ambulatory ulcer regimen
60	8	New gastric ulcer not well controlled with salicylate withdrawal and ambulatory ulcer regimen
53	2	Reactivation of old duodenal ulcer controlled by ambulatory ulcer regimen
		Development of hypertension (diastolic over 90) in absence of pre existing hypertension on ACTH in 3 on cortisone in 10
		Hyperglycemia in 7 (fasting blood sugar above 120)
		Significant glycosuria in 2 (1 diabetic before treatment) both on cortisone
		Acne in 2 1 on ACTH 1 on cortisone
		Inflammatory parotitis in 1 on cortisone
		Ecchymoses in 5 4 on cortisone 1 on ACTH
		Undue mental hyperreactivity in 3 1 on ACTH 1 on cortisone 1 on both
		Hypokalemia (serum K below 3 4 mEq /l) in 3 on ACTH and 1 on cortisone
		Amenorrhea in 3 2 on cortisone 1 on ACTH

ministration of a hormone with definite potentialities for danger is justified in this type of patient Secondly it is possible to control the symptoms of the early severe case and to minimize the development of deformities This statement is made with some hesitation since it is so difficult to predict the course of the disease in the early case However at this writing if it is felt that a severe rheumatoid arthritis is developing induced hyperadrenalism seems worth starting Third the average patient with rheumatoid arthritis who is moderately crippled can be made much more comfortable by administration of these hormones but the cost of the hormone the cost of the medical care and the anticipated hazards must be weighed against the benefits to be expected Lastly there is the severe patient crippled and bedridden with rheumatoid arthritis and requiring rehabilitory measures He is the main problem Much can be accomplished with physical medicine particularly with exercises beyond pain and fatigue limits Some benefits may be achieved with orthopedic surgery but the time effort and expense involved are not commensurate with the benefit obtained The experience of 2 or 3 more years will be necessary before this question can be decided

Can or should sustained treatment be continued indefinitely? In our opinion at least this is possible provided the vicissitudes necessitating periods of withdrawal are recognized many such vicissitudes may be anticipated

Variants of Rheumatoid Arthritis

Patients with juvenile rheumatoid arthritis apparently respond to the administration of these hormones in a manner similar to that seen in adult rheumatoid arthritis However cortisone has a retarding effect upon growth in young animals and the advantages and disadvantages of long continued administration of these hormones to a growing child must be carefully weighed before such therapy is instituted Patients with Marie Strumpell disease respond much like those with typical peripheral joint rheumatoid arthritis so do patients with arthritis associated with psoriasis In general larger amounts of hormone are required to control the psoriasis than the arthritis

DEGENERATIVE JOINT DISEASE (OSTEOARTHRITIS)

The symptoms of degenerative joint disease are beneficially modified by the administration of cortisone or ACTH with a decrease in

pain followed by some increased mobility of the affected joints Usually symptoms recur when hormones are stopped but much less abruptly than is the case with rheumatoid arthritis However the use of these hormones in an age group in which elderly patients predominate is open to some criticism since many of the untoward effects are more prone to occur in the older age group than in young individuals Most of the symptoms of degenerative joint disease can be modified by simple palliative measures Use of these hormones has seemed worth while only in degenerative joint disease of the hip (malum coxae senilis) We have treated 12 patients with this syndrome with cortisone and have noted a beneficial effect But as was to be expected with elderly patients half of them were unable to continue the hormone for longer than 3 months So far, it is questionable whether cortisone or ACTH therapy should be considered in degenerative joint disease since in most instances the prognosis is excellent with far simpler and less heroic measures

SHOULDER HAND SYNDROME

The shoulder hand syndrome is of unknown etiology but is often associated with a pre existing myocardial infarction or a frozen shoulder due to local causes such as bursitis The symptoms of this syndrome have responded to the administration of cortisone In certain instances after long continued use of cortisone there was no recurrence of symptoms when the hormone was withdrawn This is considered a self limited disease and the use of these hormones in conjunction with physical medicine may be very helpful Acute shoulder bursitides respond excellently to hormone administration, but whether the beneficial effects will continue following withdrawal depends upon the duration of the underlying disease In certain instances of bursitis about the shoulder acute symptoms persist for only 5 or 6 days and hormone administration for this period of time may result in an absence of recurrence after withdrawal of the hormone

RHEUMATIC FEVER

A great deal of controversy now revolves about the use of these hormones in rheumatic fever A word must first be said concerning the natural history of this disease which is even more varied than that of rheumatoid arthritis The onset may be abrupt or smouldering Inflammation may involve the joints the myocardium pericardium or

endocardium or a combination of these four sites The inflammatory process may persist in one site or another for varying periods of time Inflammation may involve the endocardium or myocardium alone leading to scarring but without a general systemic reaction and with no clinically recognizable attack of acute rheumatic fever There is no known method by which the course of the disease in a given case may be predicted and it is therefore difficult to evaluate therapy Salicylates have been used for 75 years in the treatment of rheumatic fever and although the arthritic symptoms of the rheumatic patient usually respond satisfactorily to salicylates there is no unanimity of opinion concerning their efficacy in rheumatic carditis

Following the administration of cortisone or ACTH in rheumatic fever the inflammatory reaction is modified beneficially for the patient Fever tachycardia and joint inflammation subside promptly sedimentation rate reverts to normal and the PR interval when prolonged often falls to normal levels However when the hormone is withdrawn if activity of the disease persists all these signs and symptoms recur It is practically impossible to determine the persistence of disease activity before withdrawal of the hormone There have been reports that in very early cases a period of 7 to 10 days of hormone administration has not been followed by relapse in symptoms when therapy is stopped (32) There have been other reports concerning essentially similar patients who have passed through the usual course of rheumatic fever with the development of carditis in a fashion similar to that seen with customary treatment such as salicylates and bed rest (30) A cooperative study is now in progress in this country and in England on the use of these hormones in rheumatic fever The study is well controlled and some answer to this vexing problem should be forthcoming in about 2 years In this study 6 weeks of hormone administration have been adopted as the period which should cover the disease activity of most patients with rheumatic fever for in the great majority of patients a subsidence of activity within 6 weeks of onset of the disease may be expected It is hoped that by ACTH administration for 6 weeks the inflammatory process may be so modified that the stigmata of rheumatic heart disease may not develop With the scattered reports now available it is impossible to say with certainty that the administration of these hormones will prevent cardiac damage —the obvious problem in rheumatic fever

To hope that widespread use of these hormones will eventually result in the disappearance of rheumatic heart disease is somewhat of

an absurdity since a large number of patients with rheumatic heart disease observed with congestive failure in later life have no history of an acute attack of rheumatic fever In this group of patients no prophylactic administration of cortisone or ACTH can be contemplated since there is no acute episode to treat It seems reasonable that for full blown rheumatic fever the use of cortisone or ACTH for 6 weeks should be considered to control the inflammatory lesion completely during that period of time The inflammatory process may not have involved the heart before treatment is instituted and may have subsided before hormone is withdrawn This program should be undertaken if feasible It is generally agreed that during the administration of these hormones in acute rheumatic fever all previously advised measures should be continued such as bed rest and careful observation of the patient including electrocardiography and roentgenography There is no need for salicylates Fortunately this program does not raise the problem of sustained hyperadrenalism which is of major concern in rheumatoid arthritis in the majority of instances a 6 week period of therapy should be adequate

OTHER DISEASES

Lupus Erythematosus Disseminatus

Lupus erythematosus disseminatus is a disease involving the connective tissue in an inflammatory process with a special predilection for small blood vessels and the endocardium It is usually fatal within 5 years Among 50 patients seen in the Presbyterian Hospital only 2 spontaneous remissions occurred lasting for more than a year Other clinics have seen spontaneous remissions more frequently but they have not been long lasting and evidence of activity of the disease persisted although the patient was symptomatically much improved Since the inflammatory process involves small blood vessels throughout the body many systems are involved leading to a multiplicity of symptoms which generally are beneficially modified by the administration of cortisone or ACTH When the disease is very severe more hormone is needed as is the case with all the inflammatory processes which are modified to the benefit of the patient by therapy with these hormones In many instances disseminated lupus may be treated on a long term basis by cortisone or ACTH Again one is faced with the problem of sustained hyperadrenalism with all the dangers that that entails It has been a common experience that if a renal lesion is present manifested

by hematuria albuminuria or a fixed specific gravity the lesion may become more severe during administration of these hormones to the detriment of the patient This is probably related to the healing process after the inflammation has subsided whereby vital areas of renal parenchyma become infarcted Therefore renal disease is a contraindication to the use of these hormones in disseminated lupus One of the unpleasant end results of hormone treatment of lupus is the appearance of renal insufficiency when the patient is apparently doing quite well

Discoid lupus as well responds to cortisone or ACTH Discoid lupus may merge into a disseminate lupus much more frequently than was originally thought and it hardly seems wise to differentiate between the two diseases The "rebound phenomenon discussed in the section on rheumatoid arthritis may be seen following hormone withdrawal in disseminated lupus For this reason we have hesitated to treat a patient with mild disease because of the possibility that the mild disease may develop into a severe one for an indefinite period of time following withdrawal

Periarteritis Nodosa

The symptoms of periarteritis nodosa a disease involving larger blood vessels than those involved in lupus erythematosus disseminatus will respond as well to the administration of cortisone or ACTH It has been noted (2) that during healing of the inflammatory vascular lesion large vessels may be shut off resulting in infarctions in various areas particularly in the kidney with resulting renal insufficiency In a few instances patients with periarteritis nodosa have been maintained for long periods of time relatively symptom free by the use of cortisone or ACTH

Dermatomyositis

Dermatomyositis is a syndrome involving the skin and skeletal muscles in an inflammatory reaction of unknown etiology There have been reports in the literature that a remission has followed the administration of cortisone or ACTH (22) In our experience this remission has been extremely variable We have treated 5 patients 2 with an increase in muscle strength up to a certain point but followed during continued hormonal administration by a marked increase in weakness 1 with a very dramatic temporary improvement following a

short course 1 with no symptomatic improvement and 1 who required such large amounts of hormone as to render impractical continued treatment This syndrome is difficult to differentiate from lupus and scleroderma except by exclusion

Scleroderma

To a certain extent the symptoms of scleroderma have responded to the administration of these hormones, but the course of the disease is so chronic, and the amount of hormone required to produce a beneficial effect so great, that it has not been feasible to continue many patients for long periods of time on such large doses of hormone The ventilatory insufficiency associated with the pulmonary lesions of scleroderma has not been materially benefited even in early cases by large amounts of hormone ACTH and cortisone do not appear to be practicable for the control of severe scleroderma

Gout

The best treatment for acute gout continues to be the administration of colchicine However at times the acute attack may fail to respond to adequate doses of colchicine and in such instances 2 to 3 injections of 50 mg of ACTH at 4 to 5 hour intervals during the course of the treatment with colchicine have proved efficacious Acute gout may respond as well to ACTH alone but following withdrawal of the hormone symptoms usually recur For this reason ACTH should be given in conjunction with colchicine It is the feeling of many who work in this field that in acute gout, ACTH for an unknown reason is more effective than cortisone The treatment of chronic tophaceous gout should continue to be a maintenance dose of colchicine and a uricosuric agent such as benemid In rare instances chronic tophaceous gout may be controlled by sustained cortisone administration in a manner similar to that of rheumatoid arthritis but the general experience with this form of therapy has not been favorable Chronic tophaceous gout should not be considered a suitable disease for treatment with these hormones

Leukemia and Lymphoma

Our experience with the treatment of leukemias and lymphomas with cortisone or ACTH has been meager in comparison with that of

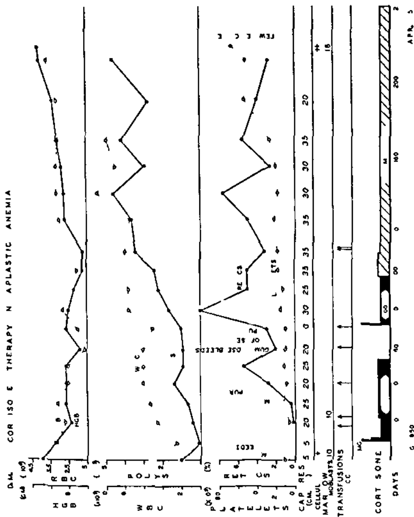


FIG 1 —Cortisone therapy in aplastic anemia

others However in general in the patient with acute leukemia or a lymphoma the effect of induced hyperadrenalism upon the disease is beneficial only temporarily and the patient becomes refractory to the continued administration of hormone

PURPURA

ACTH and cortisone have a very definite effect upon capillary permeability In our experience when capillary permeability has been

short course 1 with no symptomatic improvement and 1 who required such large amounts of hormone as to render impractical continued treatment This syndrome is difficult to differentiate from lupus and scleroderma except by exclusion

Scleroderma

To a certain extent the symptoms of scleroderma have responded to the administration of these hormones, but the course of the disease is so chronic, and the amount of hormone required to produce a beneficial effect so great, that it has not been feasible to continue many patients for long periods of time on such large doses of hormone The ventilatory insufficiency associated with the pulmonary lesions of scleroderma has not been materially benefited even in early cases by large amounts of hormone ACTH and cortisone do not appear to be practicable for the control of severe scleroderma

Gout

The best treatment for acute gout continues to be the administration of colchicine However at times the acute attack may fail to respond to adequate doses of colchicine and in such instances 2 to 3 injections of 50 mg of ACTH at 4 to 5 hour intervals during the course of the treatment with colchicine have proved efficacious Acute gout may respond as well to ACTH alone but following withdrawal of the hormone symptoms usually recur For this reason ACTH should be given in conjunction with colchicine It is the feeling of many who work in this field that in acute gout, ACTH for an unknown reason, is more effective than cortisone The treatment of chronic tophaceous gout should continue to be a maintenance dose of colchicine and a uricosuric agent such as benemid In rare instances chronic tophaceous gout may be controlled by sustained cortisone administration in a manner similar to that of rheumatoid arthritis but the general experience with this form of therapy has not been favorable Chronic tophaceous gout should not be considered a suitable disease for treatment with these hormones

Leukemia and Lymphoma

Our experience with the treatment of leukemias and lymphomas with cortisone or ACTH has been meager in comparison with that of

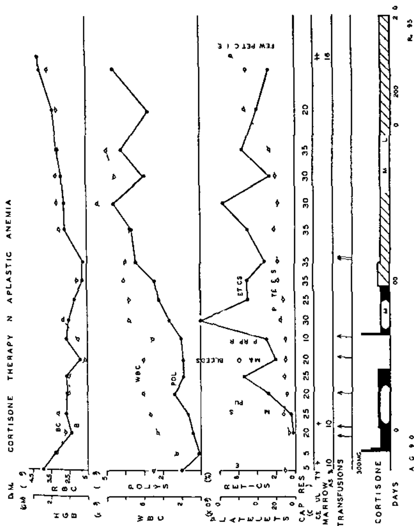


Fig 1 —Cortisone therapy in aplastic anemia

others However in general in the patient with acute leukemia or a lymphoma the effect of induced hyperadrenalism upon the disease is beneficial only temporarily and the patient becomes refractory to the continued administration of hormone

Purpura

ACTH and *cortisone have a very definite effect upon capillary permeability* In our experience when capillary permeability has been

increased due to thrombocytopenia or in radiation purpura without a thrombocytopenic element it becomes normal or much decreased on sustained administration of these hormones Following withdrawal of the hormone in most instances the permeability again becomes increased (Fig 1) This is somewhat paradoxic, since one of the manifestations of Cushing s syndrome is easy bruisability associated at times with purpura We have seen numerous instances of ecchymoses in patients during sustained hyperadrenalism In such patients capillary resistance has been normal as measured by the Daldorf pump there has been no thrombocytopenia and prothrombin times plasma vitamin C levels and bleeding and clotting times have been normal We are at a loss to explain the etiology of these ecchymoses They are transient and apparently have no relation to trauma Because of their evanescent nature when untreated claims as to the efficacy of therapy on bleeding tendencies during induced hyperadrenalism are difficult to evaluate

Pulmonary Insufficiency

There have been some favorable reports on the use of cortisone or ACTH in pulmonary insufficiency associated with pulmonary granulomatosis particularly pulmonary berylliosis (20 31) We have 1 patient who has a diffuse fibrosis of unknown etiology with marked arterial oxygen unsaturation who required 50 per cent oxygen in a tent for survival On very small amounts of cortisone (37 5 mg a day of the oral preparation) she is able to perform her daily duties as a housewife including the care of her two children This effect is completely unexplained since permission for lung biopsy was not obtained Pulmonary insufficiency resulting from emphysema or fibrosis has not responded to hormone administration with similar dramatic results

Inflammatory Reaction

The effect on the inflammatory reaction has been studied extensively in disease states Kass *et al* (19) have administered ACTH or cortisone to patients with primary atypical pneumonia and pneumococcal pneumonia They report that although patients were undergoing a severe bout of primary atypical or pneumococcal pneumonia in the latter instance with a bacteremia they were walking around the ward feeling well and symptom free Similar observations have been recorded in pulmonary tuberculosis Woods (33) has shown that there

is no reaction to or localization of the tuberculous process which tends to spread widely Laryngeal tuberculosis has healed during the administration of cortisone or ACTH (29) However it is considered poor clinical practice at the present time to allow tuberculous lesions to be exposed to the influence of prolonged hyperadrenalism

Addison's Disease

Adrenal insufficiency (Addison's disease) has been controlled effectively with cortisone Cortisone should probably be used in conjunction with liberal amounts of salt or with desoxycorticosterone and salt since the salt losing capacity of the hypoadrenal individual is not adequately controlled by cortisone alone We have had patients in whom under cortisone therapy a moderately severe Addisonian crisis developed due to loss of salt Only in Addison's disease do tuberculous lesions appear not to represent a contraindication to cortisone since the individual is made euadrenal rather than hyperadrenal at a euadrenal level this individual is able to produce an adequate inflammatory response and perhaps thereby localize the tuberculous process

✓Asthma

Severe bronchial asthma which has failed to respond to the usual clinical measures will almost invariably respond to the administration of ACTH or cortisone The recurrence of symptoms following hormone withdrawal will depend as in the inflammatory reactions described above on the persistence of the initiating cause for the asthma In some patients with severe and persistent asthma the induction of sustained hyperadrenalism must be considered

✓Dermatologic Conditions

Urticarial and vascular reactions to foreign proteins such as antitoxin and penicillin have been said to be modified during induced hyperadrenalism (4) In other reports no beneficial results have been noted (28) In this instance again one must repeat a time worn adage —the degree of hyperadrenalism required to modify a given reaction depends upon the extent of the stimulus With a large stimulus large degrees of hyperadrenalism induced by large amounts of hormone are necessary With a smaller stimulus smaller amounts of hormone will be effective

Skin reactions to gold therapy have improved dramatically with cortisone or ACTH treatment These reactions may take months to subside spontaneously In one instance in our clinic cortisone had necessarily to be continued for 5 months before withdrawal could be undertaken without recurrence of the rash Thus in gold dermatitides one may be faced with the necessity for sustained hyperadrenalism

The use of these hormones in other dermatologic conditions has received wide attention but our experience in this field does not warrant a detailed discussion of this problem The same policies apply if the disease is chronic, sustained hyperadrenalism is required for control If sustained hyperadrenalism is required minimal degrees of it

TABLE IV

Response of Dermatologic Diseases to Cortisone or ACTH

Beneficial	Nonbeneficial
Pemphigus	Epidermolysis bullosa
Exfoliative dermatitis	Acne
Urticaria and angioneurotic edema	Herpes simplex
Allergic (atopic) eczema	Varicella
Psoriasis	Kaposi s hemorrhagic sarcoma
Contact dermatitis	Local application to psoriatic plaques
Nummular eczema	
Lichen planus	
Dermatitis herpetiformis	
Drug eruptions	
Seborrheic dermatitis	

are relatively safe and maximal degrees of it are as unsafe in skin diseases as in other conditions The same difficulties arise in sustained hyperadrenalism in dermatology as in other branches of medicine The response of skin diseases to hormone administration is given in Table IV Local application of cortisone to the skin lesions of psoriasis has failed to control this disease

Eye Conditions

In the eye alone it has been possible to create a local area of hyperadrenalism without systemic hyperadrenalism by the use of eye drops and subconjunctival injections of cortisone Inflammatory diseases of the anterior parts of the eye with an allergic component apparently respond to such local applications But for the posterior regions general hyperadrenalism is required here the same principles apply as for chronic or acute inflammatory processes elsewhere and the advisability

of minimal degrees of hyperadrenalism if sustained for long periods of time Detailed reviews of this problem have appeared in the literature (21 34)

BURNS

There is at present considerable disagreement concerning the efficacy of induced hyperadrenalism in the treatment of acute burns It is possible that the fibrotic reaction leading to contractures may be minimized but scepticism is fairly general as to the value of cortisone or ACTH in modifying the toxic reactions to a severe burn Much more work on this subject is required before this controversy can be resolved

SUMMARY

In the euadrenal individual the administration of cortisone or ACTH will lead to a certain degree of hyperadrenalism the degree depending on the amount of hormone administered The response of the host to an inflammatory stimulus will be modified by hyperadrenalism the degree of modification depending upon the amount of hyperadrenalism induced Inflammatory stimuli may lead to detrimental effects in the host as is manifest in rheumatoid arthritis These detrimental effects of the inflammatory reaction can be modified beneficially for the host by the administration of cortisone or ACTH In other inflammatory stimuli the host reaction is necessary to control the offending agent but during hyperadrenalism the reaction of the host is depressed and with no control the stimulus may go unchecked In such instances hyperadrenalism is detrimental to the host

The induction of hyperadrenalism rarely modifies the offending agent but affects only the reaction of the host to that agent If the agent persists once hyperadrenalism is terminated the host again responds in characteristic fashion and symptoms recur If the agent is no longer present symptoms do not recur In many instances the agent persists and to achieve an effect beneficial to the host sustained hyperadrenalism must be undertaken But many circumstances arise in the course of months or years in which the host s reaction to an offending agent is of benefit to the host When this occurs hyperadrenalism should probably be terminated and hyperadrenalism should be kept at minimal levels in order to detect the presence of such agents

The other metabolic effects of induced hyperadrenalism also constitute a hazard to short or long term administration These occasion

ally require termination of the hyperadrenal state but at all times constant vigilance on the part of the physician is essential to avoid untoward developments In most instances the appearance of detrimental effects is related to the degree of hyperadrenalism induced and for this reason as well it should be maintained at minimal levels

In the group of diseases discussed it is difficult to evaluate cortisone and ACTH as therapeutic tools even after a clinical experience of 30 months One can only recount events so far experienced and wait for a period of years to make a final evaluation

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Abnormal Proteins in Myeloma

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INTRODUCTION

FROM THE pathophysiologic point of view the most interesting part of the myeloma problem is the disturbance of protein metabolism Errors of metabolism of many different substances have long been known Many of these have aptly been named chemical malformations or inborn errors of metabolism (53) as they are obviously caused by hereditary factors The study of these maladies has contributed considerably to the understanding of the genetic control of the metabolism of uric acid amino acids porphyrins carbohydrates and lipids

As yet inborn errors of metabolism due to a genetic factor influencing protein metabolism have not been described The author has collected available data on a large number of myeloma patients from the province of Upland in Sweden in an effort to establish familial connections between these patients The result was entirely negative Our knowledge of symptomatic changes in blood proteins is fragmentary but it is hoped that a study of characteristic protein changes with modern chemical physicochemical and serologic methods—if correlated with other changes—will reveal additional material for a fruitful discussion of the hyperproteinemia in myeloma and in other diseases

It is now generally recognized that multiple myeloma is a disease in which a disturbed protein pattern—or to use Snapper's (128) expression the protein spectrum —in the blood is often a characteristic feature

Even with electrophoresis and ultracentrifugation it has not been possible to differentiate clearly between several of the subfractions of

the electrophoretic components Much new and valuable information will be gained from fractional electrolyte precipitations under well defined conditions (temperature *p*H etc) as has been done by Butler and Montgomery (27) Derrien (38) and recently by Effersoe (45) Future progress in this field may depend also on the development of certain serologic methods These methods are already gaining increasing importance e g for the determination of albumin and lipoprotein (28 73 75) Detailed analysis of the amino acids with the aid of paper chromatography and microchemical methods will also aid in the chemical characterization of abnormal proteins (37)

The limitations of routine determinations by electrophoresis and ultracentrifugation are so obvious that they need hardly be emphasized In this connection the costliness of the apparatus the time consuming calculations the need for well trained technicians and critical and competent physical chemists may be mentioned Pedersen (106) has stressed that the large number of investigations with the aid of electrophoresis may lead to the publication of many uncritical experiments Just as valuable as this method is in the hands of the person who knows the technique and is familiar with its many sources of error by so much is it dangerous in the hands of persons who know only a little about it

It is because of these difficulties that efforts are constantly being made to replace the more intricate methods of electrophoresis and ultracentrifugation with combinations of some of the following technics (*1*) dilution test (euglobulin) (*2*) measurements of serum density (*3*) gelification tests (*4*) colloid stability cadmium tests etc (*5*) viscosity determinations (*6*) precipitations with electrolytes etc (*7*) electrophoresis on paper (*8*) ultraviolet absorption (*9*) serologic methods Unfortunately these efforts have been only partly successful and electrophoresis and ultracentrifugation remain the methods of choice for the complete analysis of the serum proteins *

ELECTROPHORESIS

In his classic investigation on electrophoresis Tiselius (143) divided the protein components of the serum into four groups which could be distinguished according to decreasing rate of migration namely

* The results of the following investigations were obtained in close co-operation with Dr K O Pedersen of the Institutes of Biochemistry and Physical Chemistry University of Upsala Sweden

albumin and alpha, beta and gamma globulin (Fig 1) It was soon found that the gamma globulin fraction contains the major portion of the antibodies Thus interest in the gamma globulins has increased considerably particularly since the methods of Cohn (29) have made it possible to isolate active fractions Protein solutions containing chiefly gamma globulins are now available and are used as prophylactic agents against a number of virus infections (89 134)

A detailed analysis of electrophoretic diagrams reveals that "the gamma globulin" is not uniform but may sometimes be split into a $gamma_1$ and gamma fraction The same holds true of the alpha and

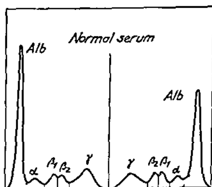


Fig 1 —Electrophoretic diagram of normal serum with typical division of beta fraction into beta and beta

beta fractions The preparation of gamma globulins in a purified state has shown that substances with varying functions and probably with different chemical properties all belong to the large group of gamma globulins The designation gamma fraction containing a large number of different proteins or "gamma globulins" is therefore in order

Serum proteins in myeloma were first examined with the aid of electrophoresis by Longsworth *et al* (86) The early workers demonstrated that the gamma fraction is unusually large Gutman *et al* (58) determined serum euglobulin" and "pseudoglobulin I and II" in 38 patients with myeloma They used the salting out method of Howe and examined in addition some of these hyperglobulinemic serums electrophoretically Two main groups were found (*1*) 4 cases in which the beta fraction was dominant (*2*) 3 cases with a large gamma fraction Kekwick (72) found the gamma globulin fraction to be predominant in 4 of 5 cases in the fifth there was a high beta fraction

Gutman *et al* also noted that in certain cases of myeloma the serum proteins were apparently normal The fractions obtained with the *Howe technic did not correspond with the electrophoretic pattern* Later Wuhrmann and Wunderly (158) confirmed the presence of two main types of electrophoretic pattern in myeloma—the gamma type and *beta type—but noted additional cases of myeloma with a normal elec* trophoretic composition of the serum These authors have recently de scribed a number of cases which they regard as instances of alpha *myeloma* (159)

Alpha Myeloma

Ludin (87) reported 2 cases of alpha myeloma giving clinical data and electrophoretic analysis The increase in alpha globulin was very moderate (9 6 to 11 4% of total protein in the first case 12 5% in the second) and the values for total protein were normal Alpha myeloma was found in 12 of 60 cases by Wuhrmann *et al* (159) These workers state that the course of the disease in patients with this type of mye loma is very rapid and malignant Unfortunately the clinical data on these cases are incomplete They described 2 clear cut cases in detail The serum of 1 patient contained 23 per cent alpha globulin (total pro tein 5 4 Gm 100 cc) There was no Bence Jones protein In a case observed by Sandkuhler (121) in Heidelberg there was a diffuse im mature plasmacytoma which had spread throughout the skeleton Bence Jones protein was present In the peripheral blood 10 000 white blood cells were found with 6 5 per cent plasma cells The formol gel test was negative The cholesterol content of the serum was 160 mg per 100 cc the total protein 8 5 Gm per 100 cc with 53 per cent alpha globulin Postmortem examination was not performed

Aside from those just cited there are no well documented cases of alpha myeloma in the extensive material on electrophoretically analyzed *myeloma serums (1 68 100) Soulier (133) describes a patient* with a total protein of 14 6 Gm per 100 cc and a globulin content of 11 6 Gm per 100 cc No sternal puncture was performed and the pres ence of Bence Jones protein is not mentioned The roentgenograms disclosed osteolytic areas with diffuse decalcification of the entire skeleton and collapse of the fifth dorsal vertebra The clinical diag nosis of myeloma was evident Unfortunately the electrophoretic dia gram of this case is difficult to interpret The author himself remarked that a compensating current should have been used to obtain better separation of the fractions

It is not clear why only certain workers report cases of myeloma with a high content of alpha globulin in the serum whereas other clinicians never encounter such cases There may actually be a geographic difference and alpha myeloma may occur with special frequency in Switzerland In the cases described by Ladin the clinical picture of alpha myeloma is not atypical Until now our group in

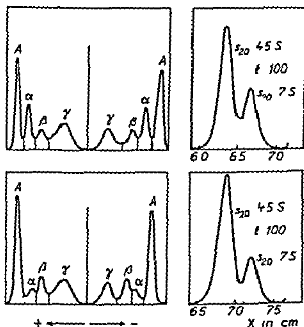


FIG 2 –Electrophoretic (left) and ultracentrifugal (right) diagrams of a serum with high alpha globulin content Clinical picture was first interpreted as myeloma Later all symptoms disappeared among them the marked increase in alpha globulin Obviously such conditions are difficult to interpret correctly

Upsala and Malmo has never found a case of myeloma with a high alpha globulin content of the serum The same holds true for Olhagen who has had a wide experience in the electrophoretic analysis of the serum proteins in myeloma

Among the cases with hyperglobulinemia examined by Pedersen and myself one serum showed a considerable content of alpha globulin (Fig 2) Although the diagnosis of myeloma was seriously considered continued observation showed that this diagnosis was incorrect and that an unrecognized infection must have caused an increase in serum globulin of the alpha type It should be emphasized that an infection

or even generalized carcinomatosis (31) may simulate not only the bone marrow picture (117) but also the hyperglobulinemia of myeloma Prolonged observation is necessary before the publication of reports of such cases is justified

Beta Myeloma

The first electrophoretic analyses of myeloma serums by Longsworth *et al* Kekwick and Gutman *et al* demonstrated an increase in the beta globulins in many cases of multiple myeloma This has been amply confirmed by other workers Wuhrmann *et al* (159) found an increase in this fraction in 25 of 60 cases examined All other authors with extensive experience have found a lower percentage The Swiss investigators divide their cases of beta myeloma into two groups one containing a beta the other a beta fraction The cases with large amounts of beta globulin usually show a considerable decrease of the gamma fraction This is the reason why some authors have confused the beta fraction with gamma globulins Graphic plotting of the migration velocities against the normal variations of velocity as shown in Figure 3 allows correct diagnosis of the different fractions The beta, myelomas of Wuhrmann *et al* correspond to the cases we designate as beta myeloma (Fig 3) They comprise 10 of the total of 60 cases This percentage corresponds with that found by other workers (1 68 94)

The clinical picture of beta myeloma is in no way different from the classic one It is usually impossible to distinguish between gamma and beta myeloma without electrophoresis

An increased beta fraction is known to occur principally in certain cases of myeloma and biliary cirrhosis We have seen it also in 1 case of chronic unexplained kidney disease in which the autopsy did not reveal the presence of myeloma (see Fig 6A) Since the beta fraction contains most of the lipoproteins considerable lipemia might be expected when the beta fraction is increased This is actually the case in primary biliary cirrhosis in which the marked increase of the beta globulin fraction is often accompanied by high serum lipids In certain instances of this disease the serum may remain limpid because the phospholipids of the serum are also increased (4) sometimes even as high as 1 600 to 2 800 mg per 100 cc

We have observed only 1 case of myeloma with an increased beta fraction and marked lipemia—a very rare occurrence The patient was

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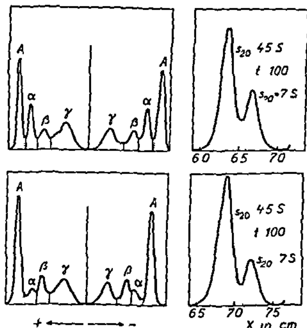


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ulin 5 9 per cent A marked increase in the beta fraction was disclosed by electrophoresis

The serum was opaque and milky even in the fasting state After standing for 24 hours a white layer had formed and was floating on the surface The total cholesterol was 580 mg per 100 cc on one occasion and 570 mg on another The basal metabolic rate was + 12 per cent The results of serum bilirubin alkaline phosphatase cephalin flocculation and thymol turbidity tests were normal A detailed analysis of the serum lipids showed marked lipemia (Table I)

The patient subsequently died in uremia with severe anemia The autopsy revealed myelomatosis and nephrosis with hyaline casts in

TABLE I

LIPEMIA IN A CASE OF BETA MYELOMA

Serum Lipids	Sample 1 mg/100 cc	Sample 2 mg/100 cc	Normal Values (Thannhauser) mg/100 cc
Total lipids	1 620	1 900	
Total phospholipids	345	318	150–250
Lecithin	195	232	100–200
Cephalin	49	0	
Sphingomyelin	101	83	10–30
Cholesterol free	79	105	40–70
Cholesterol total	311	254	150–260
Cerebrosides			
Neutral fat	680	730	
Fatty acids	280	603	

the tubules The bone marrow was replaced by small plasma cells This type of cell is usually found in cases of beta myeloma although we have observed at least 1 case of beta myeloma with large myeloma plasma cells Incidentally no deposits of cholesterol were found in this case

The lipid metabolism in beta myeloma has so far received little attention but it is certainly an important problem for future research Hartmann (61) has noted a moderate increase in cholesterol in beta myeloma Cremer (32) has reported on 1 patient with reticulosis who showed osteolytic foci up to the size of a walnut and Bence Jones proteinuria Marked lipemia was noted with a total cholesterol of 355 mg per 100 cc and 648 mg per 100 cc of "total fat Brehmer and Lubbers (25) observed a patient with diffuse xanthomatosis of the bones essential hyperlipemia and generalized proliferation of plasma cells in

Kindly performed by Dr Brante

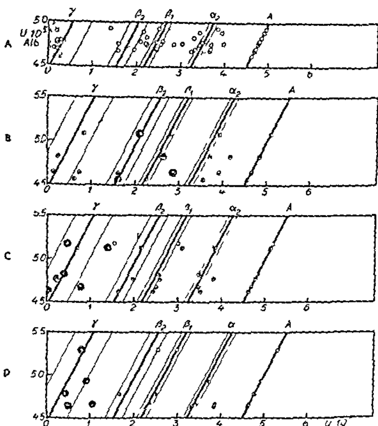


Fig 3—Graphic representation of electrophoretic mobilities for the various protein components plotted against albumin mobility A lymphogranuloma venereum 11 cases B beta myeloma 4 cases C gamma myeloma 6 cases D macroglobulinemia 5 cases Pathologic component in each serum is marked by extra circles Thin lines represent the zone of plus or minus twice the standard deviation As can be seen the alpha fraction always shows a large variation In beta myeloma 1 patient has a definitely pathologic beta fraction the rest are beta or beta In gamma myeloma and macroglobulinemia the beta component has normal mobility whereas the gamma fraction has abnormal mobility in several instances In lymphogranuloma venereum gamma globulins are all in the normal zone (153)

a 50 year old woman with typical myeloma as revealed by roentgenograms sternal puncture and urinary Bence Jones protein She did not have jaundice or xanthomas The sedimentation rate was 142 mm in 1 hour hemoglobin 60 per cent red blood cells 2 900 000 per cubic millimeter nonprotein nitrogen 50 mg per 100 cc The total serum protein was 8 6 Gm per 100 cc with albumin 2 7 per cent and glob

certain whether the differences between various protein fractions are sufficiently marked to be of practical value

ULTRACENTRIFUGATION

A characteristic property of any given protein is its sedimentation constant in the ultracentrifugal field If other factors such as the diffusion constant are known the molecular weight can be calculated from the sedimentation constant Thus it has been possible to group various proteins according to their molecular size With the ultracentrifuge as constructed by Svedberg the sedimentation of different components in a mixture can be followed during the centrifugation A number of photographic exposures made during centrifugation register the process of sedimentation and a curve may be obtained showing the order in which the different components are selectively forced down (108 136 137) The heaviest molecules go down first followed by the others according to decreasing molecular weight in this way the different protein fractions of an unknown serum can be separated

In 1935 McFarlane (90) reported the first observations on myeloma serums with the ultracentrifugation method He observed the occurrence of two peaks one with the sedimentation constant of serum albumin (4 5 S *) and another with the higher sedimentation constant of globulin (7 S) In 1 case he also noted the development of a fraction with a constant of 11 S but the diagrams were difficult to interpret as the technic had not been fully developed

Later Kekwick analyzed myeloma serums with the ultracentrifuge and found an increase in gamma globulins In one of these a component was found which migrated faster in the centrifugal field than the S 7 component All of the others showed large S 7 *components* In another case a beta globulin was isolated electrophoretically and unfortunately proved to be nonhomogeneous in the centrifuge Because denaturation is difficult to avoid during isolation of a protein Pedersen prefers to study the proteins directly in the serum

Since 1938 Pedersen and the author have collaborated closely in a study of pathologic serum globulins with the aid of electrophoresis and ultracentrifugation Pedersen (109) has shown that normal serum always contains three main fractions The X component" which belongs to the electrophoretic beta fraction consists mainly of lipoproteins containing phosphatides It has a lower density than *albumin*

* S designates Svedberg units

the bone marrow The maximum value for cholesterol was 612 mg for phospholipids 790 mg for neutral fat 5722 mg per 100 cc! Unfortunately no analysis of the serum proteins was given The autopsy revealed large amounts both of plasma and xanthoma cells

Little is known about the function of the proteins in the beta fraction This fraction is increased in disturbances of lipid metabolism and may be decreased when the lymphatic apparatus is damaged as in lymphatic leukemia One might speculate that at least part of this fraction is produced by the lymphocytes This would support the finding of large beta fractions in a number of cases with macroglobulinemia where the bone marrow is filled with atypical lymphocytes Pedersen and Waldenstrom have pointed out that although both albumin and gamma globulin may vary considerably in different conditions the alpha and beta fractions combined only rarely decrease to any extent This may indicate that these fractions contain substances essential for the maintenance of life

Gamma Myeloma

This type of myeloma is the most common one 64 per cent of Janssen s cases were gamma myelomas This type of myeloma as well as normoproteinemic myeloma will be discussed in the section on ultracentrifugation

Paper Electrophoresis

The recent developments in paper electrophoresis (30 44 46 51 55 74 75 97 122 123 144) have not as yet been applied to myeloma This method should prove of great importance in the study of clinical abnormalities of serum proteins and in the preparation of the various protein fractions Possibly the method will also be found useful for purifying pathologic proteins before their use as antigens for the preparation of specific antiserums The amino acid pattern after hydrolysis which is now studied by microbiologic methods can also be analyzed by means of paper chromatography

OTHER METHODS OF PROTEIN ANALYSIS

The application of serologic and ultraviolet absorption methods to the investigation of serum proteins is comparatively recent and the importance of the results cannot yet be evaluated Studies on ultraviolet absorption have been published by Wunderly So far it is not

certain whether the differences between various protein fractions are sufficiently marked to be of practical value

ULTRACENTRIFUGATION

A characteristic property of any given protein is its sedimentation constant in the ultracentrifugal field If other factors such as the diffusion constant are known the molecular weight can be calculated from the sedimentation constant Thus it has been possible to group various proteins according to their molecular size With the ultracentrifuge as constructed by Svedberg the sedimentation of different components in a mixture can be followed during the centrifugation A number of photographic exposures made during centrifugation register the process of sedimentation and a curve may be obtained showing the order in which the different components are selectively forced down (108 136 137) The heaviest molecules go down first followed by the others according to decreasing molecular weight in this way the different protein fractions of an unknown serum can be separated

In 1935 McFarlane (90) reported the first observations on myeloma serums with the ultracentrifugation method He observed the occurrence of two peaks one with the sedimentation constant of serum albumin (4.5 S *) and another with the higher sedimentation constant of globulin (7 S) In 1 case he also noted the development of a fraction with a constant of 11 S but the diagrams were difficult to interpret as the technic had not been fully developed

Later Kekwick analyzed myeloma serums with the ultracentrifuge and found an increase in gamma globulins In one of these a component was found which migrated faster in the centrifugal field than the S 7 component All of the others showed large S 7 components In another case a beta globulin was isolated electrophoretically and unfortunately proved to be nonhomogeneous in the centrifuge Because denaturation is difficult to avoid during isolation of a protein Pedersen prefers to study the proteins directly in the serum

Since 1938 Pedersen and the author have collaborated closely in a study of pathologic serum globulins with the aid of electrophoresis and ultracentrifugation Pedersen (109) has shown that normal serum always contains three main fractions The "X component" which belongs to the electrophoretic beta fraction consists mainly of lipoproteins containing phosphatides It has a lower density than albumin

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* S designates Svedberg units

and gamma globulin Its sedimentation under the usual experimental conditions is therefore slower than might be expected in view of its high molecular weight Albumin with a sedimentation constant of S 4 5 comprises the largest part of the serum protein The S 7 component—mainly gamma globulin—is always much smaller

In addition to these three normal fractions a protein of high molecular weight with a sedimentation constant of 19 to 20 S is also present in many normal serums This value would probably correspond to a molecular weight of 10^6 In his study of the ultracentrifugal pattern of serum proteins Pedersen compared this normally occurring macromolecule with the pathologic so called macroglobulin" found in the disease described by us as macroglobulinemia This normal high molecular globulin has however physical properties which differ from the pathologic macroglobulin Electrophoretically it belongs to the alpha fraction whereas the pathologic macroglobulin may belong either to the beta or sometimes to the gamma fraction In some cases it may be identical with the M fraction as described by Gutman *et al* In only 1 of 20 normal serums did the high molecular fraction reach a value greater than 5 per cent of the total protein As a matter of fact a second determination of this exceptional serum revealed a value of only 3 per cent In all the other cases the value of this fraction was consistently below 5 per cent It may therefore be assumed that a S 20 globulin content of more than 5 per cent is pathologic

COMBINED ELECTROPHORESIS AND ULTRACENTRIFUGATION OF MYELOMA SERUMS

The question arises whether a specific electrophoretic pattern in different maladies always corresponds to a specific diagram in the ultracentrifuge By the combination of electrophoresis and ultracentrifugation (107 151) it has been firmly established that the gamma globulin and the S 7 component constitute the same percentage of the serum protein In addition a gamma fraction was found with a molecular weight corresponding to sedimentation constants of S 11 or in rare instances of S 19 to 20 The usual beta fraction has the common sedimentation constant found in globulins (S 7) but in a special group of cases it appears to be a macroglobulin (S 19 to 20) In 1 exceptional case in which no clinical diagnosis could be made the beta fraction was represented by a globulin with the sedimentation constant of albumin (S 4 5) Pedersen (108) has studied 1 case of

myeloma in which at low temperature the serum separated into two layers the lower containing most of the globulin The sedimentation constant of this protein varied with the concentration and temperature Such association and dissociation under the influence of concentration and temperature may perhaps explain variations found in other serums

In a large number of patients with increased gamma globulin fraction (lymphopathia venereum liver cirrhosis [chronic hepatitis] "rheumatic diseases ["collagenoses"] purpura hyperglobulinemica) a remarkable agreement existed between the gamma fraction and the S 7 component This also holds true in the few diseases in which the gamma component is lowered For instance in Cushing s disease both the gamma fraction and the S 7 component are lowered In a patient with severe hypoproteinemia after typhoid fever both the albumin and the gamma fractions were found to be low and the ultracentrifugal patterns corresponded to changes of the electrophoretic curves Thus there is good evidence that the gamma globulins are the chief proteins making up the S 7 component and furthermore that in a number of different pathologic conditions the molecular weight of the gamma globulin corresponds to that of the S 7 component (150 000)

Gamma Myeloma

Of 14 serums from myeloma patients with an increase in gamma globulin 10 showed a normal pattern on centrifugation in 3 only was an abnormal sedimentation of the dominating globulin fraction found The blood of 1 patient with the clinical picture of myeloma (Fig 4B) showed many abnormalities (e g no clot retraction) The same diagram (Fig 4B) proves that the much increased S 7 component contains a large amount of the total serum proteins and not only the gamma component In this case the serum proteins are obviously much more abnormal than is usually seen even in myeloma At first sight it might be assumed from the diagram that this patient has an increased alpha plus beta fraction which might correspond to the so called alpha plus beta plus gamma globulin of Wuhrmann and Wunderly However the upper limits for the normal alpha plus beta are not clearly defined as yet and this case may well represent an instance of a gamma myeloma of a peculiar type

In another case (Fig 4A) a slightly increased total protein content (8 5%) of the serum and a normal content of the alpha plus beta globulin fraction were found together with an increase of the gamma

fraction This patient had 32 per cent gamma globulin (normal 23% of the total protein) with two peaks on the electrophoretic diagram The ultracentrifugation pattern was remarkable It showed a normal relation between the S 4 5 and S 7 components The S 7 component in this case made up 16 per cent of the total protein (lowest normal

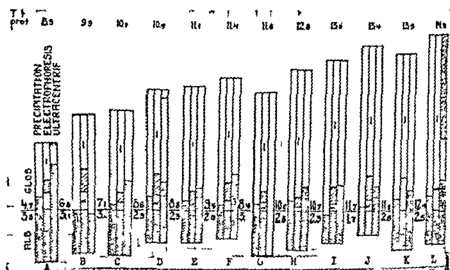


Fig 4—Graphic representation of serum protein fractions in gamma myeloma Each group of columns represents the result of triple fractionation of a single serum sample *1st column* fractionation by electrolyte precipitation (Theorell Widstrom method) into albumin and globulin *2d column* electrophoretic fractionation with beta fraction represented by oblique lines *3d column* ultracentrifugal fractionation with division into S 4 5 (lower) and S 7 components (upper) and uppermost *horizontal lines representing amount of S 20 component which is never abnormally* increased in typical myeloma The limit of albumin globulin ratio determined electrophoretically has been used as an axis to demonstrate the decrease in albumin and increase in globulin In all serums but A B and L the S 7 component and gamma fraction are of about the same size as is usually the case Serum from L contains large amounts of S 11 component

11% highest 24%) If we assume that the total *gamma fraction* should as usual belong to the S 7 component then the latter should have made up 32 per cent instead of 16 per cent of the total protein The assumption that part of this gamma fraction has a lower sedimentation constant can only be proved by the study of other comparable cases

In still another case (Fig 4L) a very high gamma globulin was present with an abnormal and unusual sedimentation constant of 11

The diagram shows clearly that this fraction alone cannot account for the total increase of the gamma globulin but that an increased quantity of gamma globulin with a sedimentation constant of 7 must also be present This indicates that even a protein with an apparently homogenous electrophoretic diagram may contain two protein fractions

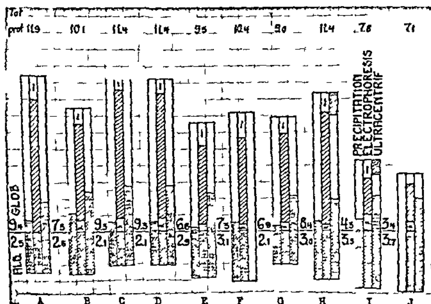


FIG 5 —Graphic representation of serum protein fractions in 6 cases of beta myeloma Symbols are same as in Figure 4 As may be seen the beta fraction usually belongs to the S 7 component In 2 cases however there is also an S 11 component (H and I) and the seemingly uniform beta fraction is thus divided into two components of different molecular size A B C and D one case E and F another case

with different sedimentation constants An S 11 component also found in some cases of beta myeloma will be discussed later

BETA MYELOMA

Since beta myeloma is a comparatively rare condition in Sweden all 6 of our cases of beta myeloma have been carefully examined (Fig 5) whereas only 14 of a much larger number of gamma myelomas has been analyzed with the methods discussed here

Among these 6 beta myelomas are 4 in which the beta fraction

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Normoproteinemic Myeloma

In many cases of so called normoproteinemic myeloma ordinary salting out technics do not reveal abnormalities in the serum proteins As already pointed out by Gutman *et al* the urine of patients with normoproteinemic myeloma often contains a considerable quantity of Bence Jones protein Pedersen and the author studied 1 case in which the total protein was only slightly elevated (8 7 Gm /100 cc) but the albumin was remarkably high when determined by salt precipitation by electrophoresis and especially by ultracentrifugation As a matter of fact 85 per cent of the proteins belonged to the S 4 5 component and 13 per cent to the S 7 component There was no proteinuria On the other hand we have seen a high S 4 5 and low S 7 content in no less than 4 of 20 normal serums

Even if the total protein value is slightly elevated the composition of the serum protein may be essentially normal In 9 of 36 cases of myeloma studied by Janssen (68) neither salt fractionation nor electrophoresis revealed any abnormality Only the relative amounts of alpha and beta globulins were slightly increased The relative amount of gamma globulin was decreased in 7 of these 9 serums Bence Jones protein was absent from the urine in only 1 case In several serums small peaks in the beta globulin pattern were found which may well indicate the presence of Bence Jones protein in the serum

Discussion

Evidently not only the gamma but also the beta fraction may consist of proteins with different sedimentation constants A coincident increase of two different globulin fractions must be extremely rare not only in myeloma but also in other conditions with hyperglobulinemia

Biologically it may well be significant that the serum proteins always belong to four classes as regards their sedimentation constants The albumin corresponds to the S 4 5 group the gamma globulin to the S 7 group Then there are pathologic S 11 components belonging to the beta and the gamma fractions These are all seen in myeloma serum However other members of the S 19 to 20 component family which may belong to the alpha beta, or gamma globulins have never been found in increased quantities in myeloma Thus it seems probable that there are certain molecular sizes that are more stable than others and that aggregations of molecules may tend to collect around the more stable centers

seemed to have the same sedimentation constant as normal gamma globulin These instances with a so called S 7 beta fraction as the dominating protein seem to be the rule not only in myeloma but also in rare cases of other diseases in which the increase in beta globulin is present (Fig 6) In 1 case of beta myeloma (Fig 5H) the greatest part of the pathologic beta globulin was contained in a very large S 7 component but more than 10 per cent of the beta globulin was present

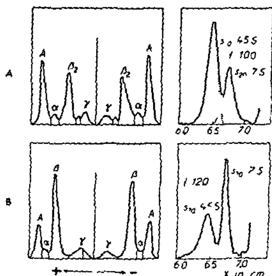


Fig 6 —Electrophoretic and ultracentrifugal diagrams of 2 serums with increased beta globulin Patient with renal failure (A) without clinical or autopsy evidence of myeloma with beta₁ fraction closely resembling that of patient with myeloma (B) Both globulins belong to the S 7 component in the ultracentrifugal analysis Note pronounced decrease in albumin and S 4 5 component in the myeloma serum (B) and absence of these changes in the serum of renal failure (A)

as an S 11 component It seems probable that the 10 per cent belongs to the pathologic beta fraction In another case (Fig 5I) the beta globulin was about equally divided between the S 7 and the S 11 components These exceptional serums seem to correspond with the previously discussed gamma myeloma where a seemingly homogeneous gamma fraction evidently contained globulins with different sedimentation constants (S 7 and S 11)

Since we have had no experience with alpha myeloma we are not in a position to discuss the sedimentation constants of the protein in this condition

The objective signs are few There is often marked pallor and sometimes considerable edema The liver and spleen are usually not enlarged but it is common to find scattered nontender enlarged lymph nodes This explains why the diagnosis of aleukemic lymphadenosis is often made There is no tenderness over the bones Roentgenograms of the skeleton do not show multiple punched out areas but a general decalcification is sometimes present which may lead to compression of a vertebra Usually there are no skeletal changes at all and slight rarefaction can be easily explained by the advanced age of the patient Roentgenologic examination does not reveal any abnormalities in the internal organs Anemia is often severe There may be slight leukocytosis and a relative increase in lymphocytes but a leukemic blood picture is never present Moderate thrombocytopenia is seen The presence in the bone marrow of large amounts of small lymphocytoid cells with shedding of protoplasm may be diagnostic The presence of tissue mast cells in the bone marrow (142) may be important in explaining the bleeding tendency The final decision rests with the ultracentrifuge

The sedimentation rate of the red blood cells is always very high and is further increased by the severe anemia There are two other simple methods of demonstrating the presence of macroglobulin in large quantities One is a strongly positive water dilution (euglobulin) test Into a test tube or glass cylinder filled with distilled water 1 drop of the serum is allowed to drop from a pipet Normally a slight haziness develops which is regarded as a 1 plus reaction Completely negative to 1 plus reactions are found in normal serums A 2 or 3 plus reaction is regarded as pathologic The latter is present when a clear cut precipitate of protein develops from the falling drop In macroglobulinemia the precipitate is usually very heavy settling down to the bottom of the vessel Occasionally the refractive index of the precipitated protein is equal to that of the water and the glass It may then be difficult to distinguish the precipitate which sediments to the sides of the glass as transparent slimy masses The protein is collected by centrifugation and redissolved in normal saline From this solution it can be reprecipitated by dilution The solubility of these proteins in electrolyte containing water and their precipitation by dilution or dialysis against water is their chief characteristic Unfortunately this test is not always positive even in the presence of large amounts of macroglobulin and a low content of macroglobulin cannot be visualized by this test

The rarity of globulins with higher sedimentation constants in multiple myeloma deserves discussion In our own 27 cases of typical myeloma there was no increase in a high molecular globulin with a sedimentation constant of 19 to 20 S that is a molecular weight of about 1 000 000 On the contrary this component was often absent from the serum This suggests that so-called macroglobulinemia which is characterized by the presence of an excessive amount of high molecular globulin must be different from myeloma Conditions giving rise to cryoglobulinemia such as disseminated lupus erythematosus may be accompanied by the occurrence of high molecular globulin (S 20 to 19) The same also holds true of certain serums from patients with nephrosis

MACROGLOBULINEMIA

A predominant increase of the S 20 component of the serum as determined by ultracentrifugation seems to occur in a rather well defined clinical picture Nevertheless considerable confusion still exists regarding its differentiation from aleukemic lymphatic leukemia plasma cell leukemia or even from myeloma Sometimes the confusion is due to the difficulties of interpreting the histologic sections of myeloma In this connection it should be emphasized that a smear obtained by bone marrow puncture sometimes gives more satisfactory histologic details than a cut section This may be one of the reasons why the difference between the histologic marrow picture in macroglobulinemia and in multiple myeloma is not always accepted The cardinal sign for the differential diagnosis is the presence of an abnormally large amount of macroglobulin in the serum as determined by ultracentrifugation A number of such cases have probably been reported under different diagnoses usually as diffuse myelomatosis

Patients with macroglobulinemia are usually elderly with a seeming preponderance of men The main complaint is not bone pain in contrast to the patient with myeloma who rarely escapes it completely The patient with macroglobulinemia suffers mainly from marked general lassitude dyspnea and bleeding from the mucous membranes The severe intractable nosebleeds often do not respond to conventional treatment More common is a slow oozing from the gums and often the patient wakes in the morning with his mouth full of blood The bleeding time is usually increased and the sites of biopsies often bleed for several days Purpuric spots have been noted but seem to be rare

mation of well circumscribed plasmacytomas the roentgenograms will at best reveal generalized decalcification In this condition pain usually is a dominant feature occasionally the pain may develop rather late Such cases have been collected by several authors (154) One of the patients with beta myeloma in the present series for several years showed only an increase of plasma cells in the bone marrow smears and hyperglobulinemia but no bone pains or positive roentgenograms After this initial period bone pains started and unequivocal skeletal lesions were later visualized on roentgenograms The first stage can hardly be designated as premyelomatous since it certainly represents the first beginnings of the disease proper If there is a true premyeloma stage changes should be present in the serum globulins before the development of skeletal lesions Assuming the existence of this condition cases with long standing hyperglobulinemia from known or unknown causes should ultimately develop into myeloma Despite careful observation of a fair number of such patients the author has never been able to confirm this sequence of events Furthermore a high sedimentation rate should be present for some years before other signs of myeloma appear if there is a premyelomatous state This is rare in our experience in fact we have observed a low erythrocyte sedimentation rate in several cases before the first symptoms of myeloma were noted The concept of premyeloma will therefore have to be dropped at least for the time Close supervision of every patient with hyperglobulinemia is essential in order to detect early signs of skeletal lesions

Essential Hyperglobulinemia

Occasionally patients are encountered with chronic hyperglobulinemia of unknown origin In view of the favorable prognosis it is important that this condition be recognized In the absence of a better designation I have chosen to call it "essential hyperglobulinemia" This syndrome should not be confused with myeloma The prognosis of essential hyperglobulinemia is not at all unfavorable as evidenced by several such cases which we have been able to follow for long periods In 1937 a thrombosis of the left central retinal vein developed in a man born in 1897 In 1945 he complained of dizziness The systolic blood pressure was 180 the sedimentation rate 93 mm in 1 hour Since then the sedimentation rate has varied between 60 and 145 mm In 1948 and 1949 attacks of pain in the legs and back were noted which later disappeared The patient also complained of hyperesthesia in the

The euglobulin test must always be combined with a determination of the relative viscosity at different temperatures Long ago Magnus Levy (92) and Albers (5) had found that the serums of patients suffering from myeloma are often very viscous A study of the viscosity with the aid of the Oswald viscosimeter was made to determine whether this method could be employed for the identification of various pathologic globulins (147 149) It was found that the determination of the relative viscosity at different temperatures may give a characteristic curve (see Fig 8) A high temperature viscosity index

$$\left(\frac{100 \times \text{rel visc } 13\text{ C}}{\text{rel visc } 37\text{ C}} \right)$$ is often found in the presence of pathologic

amounts of a protein component other than the usual gamma globulin An index of more than 120 is usually found in serums containing much macroglobulin The value for the relative viscosity of such serums is also beyond the upper limits of the normal range of variation (±2 sigma) both at 37 C and still more at 13 C (149) Among the serums that are beyond this normal zone quite a few contain pathologic serum protein components of an unusual type When the globulin is increased to 10 Gm per 100 cc or higher the viscosity also increases rapidly in the presence of a gamma component This method therefore should not be used when the total globulin is so high

Viscosity measurements are mainly important for the diagnosis of macroglobulinemia When the clinical picture is present and the dilution and viscosimetric tests are positive the diagnosis may be established with a high degree of certainty Confirmation of the diagnosis by ultracentrifugation will always be necessary

BENIGN HYPERGLOBULINEMIA OF OBSCURE ORIGIN

In patients with marked hyperglobulinemia without signs of myeloma or macroglobulinemia the author has suggested that a condition designated as premyeloma might be present This concept of premyeloma has given rise to considerable debate (111 113) The reasons are that myeloma may be difficult to recognize in its early stages and that the bone marrow picture in both acute and chronic infections may simulate myeloma (48) In the latter conditions the abnormal bone marrow as well as the hyperglobulinemia ultimately revert to normal (117)

When there is a diffuse proliferation of myeloma tissue without for

still 69 mm The patient is now working normally and there are still no signs of myeloma

We have also studied 4 women with persistently high sedimentation rates and increased gamma globulin suffering from xerostomia and/or keratoconjunctivitis sicca (Sjogren's disease) Evidently the latter syndrome is sometimes accompanied by persistent hyperglobulinemia In 1 such case there was a concomitant typical purpura hyperglobulinemica

Purpura Hyperglobulinemica

The author has observed a special type of chronic relapsing purpura in chronic hyperglobulinemia of benign nature with a marked increase in gamma globulin belonging to the S 7 component (152) The shape of the gamma peak was always broad and resembled the peak noted in lymphogranuloma inguinale (153) The extended benign course of the hyperglobulinemia with chronic purpura militates against the diagnosis of incipient myeloma Sternal puncture does not show an increase in plasma cells This syndrome too should not be confused with myeloma The type of purpura—large crops of small spots recurring in short intervals especially after exertion and leaving numerous pigmented spots—should always suggest an examination of the serum proteins It is characteristic that in these cases of essential" hyperglobulinemia it is often impossible to diagnose a "primary" disease Cases reported by Curtz (34) Humerfelt (67) Linke (83) and Oberste Lehn indicate that the syndrome is also observed in other countries Purpura may occur in myeloma The differential diagnosis between benign hyperglobulinemic purpura and symptomatic purpura in myeloma is of great practical importance in view of the favorable prognosis in the former condition

Esser (47) pointed out that there are three possible causes for purpura occurring in myeloma (1) damage to the bone marrow with secondary thrombocytopenia (2) liver damage with secondary derangement of the clotting mechanism and (3) vascular amyloidosis in the skin In my opinion purpura of unknown origin comparable to the purpura hyperglobulinemica described above could also occur in myeloma The cases reported by Lindeboom and Mulder (82) and by Esser are probably of this type but the rapidly fatal progression of myeloma precludes a prolonged course such as is found in purpura hyperglobulinemica As long as the mechanism of the increased capil

finger tips The left leg was sometimes slightly swollen In 1949 the patient noticed a brown spot on the lateral side of the left thigh and recently a similar change was noted also on the right side These skin

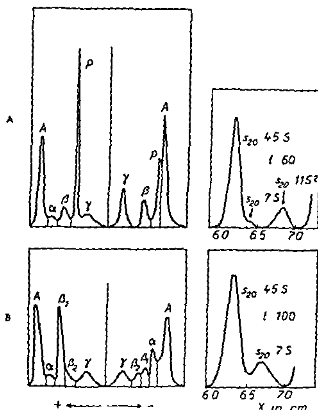


Fig 7—Unusual electrophoretic and ultracentrifugal serum diagrams of 2 patients with an undiagnosed disease and persistently increased sedimentation rate In both there is marked difference between ascending and descending boundaries In A there is a high sedimentation constant for the pathologic fraction (S 11) in the ultracentrifugal diagram in B the pathologic globulin has the low sedimentation constant of S 4 5 (= albumin)

changes were diagnosed as possibly caused by Schamberg's disease (progressive pigmentary dermatosis) The serum proteins were very abnormal (Fig 7A) The markedly abnormal proteins of another patient in whom no definite diagnosis could be made are shown in Figure 7B This man born in 1890 had an increased sedimentation rate and a slight cardiac failure in 1946 In 1951 the sedimentation rate was

Observations on spontaneously precipitating globulins in periarteritis nodosa have recently been published Since in these cases the precipitate did not dissolve on heating of the serum the presence of cryoglobulinemia has not been demonstrated beyond doubt

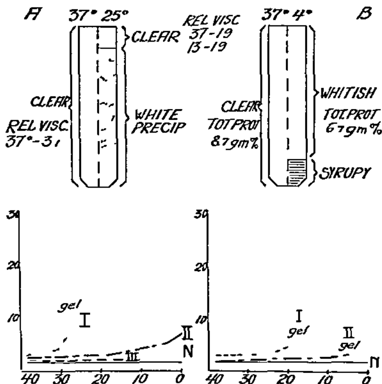


FIG 8—Different types of serum changes depending on temperature as seen on inspection and as measured in the viscometer A myeloma with cryoglobulinemia of very high degree molecular weight could not be determined for globulin precipitated on cooling N normal serum I undiluted II diluted 1 1 III filtrate free from cryoglobulin Abscissas indicate temperature ordinates relative viscosity B macroglobulinemia with typical stratification, as described in some cases an S 20 component was found in the bottom layer in 1 case and in the other an aggregation and dispersal with changing temperature

The malady in which purpura cryoglobulinemica most frequently occurs is undoubtedly multiple myeloma The condition was present in Lehmann and Flemberg s first case in Rorvik s cases (116) and in the cases reported by Barr *et al* (9) On the other hand the case reported

lary fragility in these conditions remains unknown it is hard to prove the identity of the two processes

Cryoglobulins and Purpura

A subject of frequent discussion is the association of purpura with the presence of so called *serum cryoglobulin This condition was first* described by Lehmann and Flemberg (78) Lerner *et al* (79 80) have investigated this condition and coined the name "purpura cryoglobulinemica They consider it a subgroup of Waldenstrom s purpura hyperglobulinemica *In a large number of cases of hyperglobulinemic purpura no cryoglobulin has been found in the blood In addition* the clinical picture of the two diseases is very different It should be emphasized that cryoglobulinemia can occur in the absence of hyperglobulinemia In Lerner and Watson s (79) case the total globulin content *was only 2 3 Gm per 100 cc These authors define cryoglobulin"* as "a group of proteins with the common property of precipitating (or gelifying) from cooled serum This is similar to the use of the term "Bence Jones protein" which represents a *group* of proteins precipitating at 60 C In cases in which a high concentration of cryoglobulin is *present precipitation may set in at room temperature*

The precipitation of this globulin in the small vessels of the skin on cooling *causes three types of lesions (1)* Raynaud like syndromes with bluish discoloration of ears nose and fingers (2) purpura with edema and (3) the most severe type—ulcers and necrosis of the skin with little tendency to heal In such obscure cases the erythrocyte sedimentation rate may be of considerable help Commonly when cryoglobulin is *present no sedimentation is found at zero degrees C* whereas at 37 C the sedimentation is very rapid—exactly *the reverse of the sequence in* the presence of cold agglutinins The cryoglobulin precipitates at low *temperatures* and *plugs the sedimentation tube so that the red cor*puscles *cannot form a sediment This has sometimes led to the conclu*sion that the blood in these patients clots instantaneously—*an erro*neous *interpretation of a correct observation There is no true coagula*tion since the *pseudoclot is easily soluble on warming of the plasma* or serum The presence of cryoglobulin is certain when the pseudo coagulation *is reversible with changes in temperature* Some instances of fibrinolysis in *myeloma blood may well be explained by* the presence of cryoglobulin *I have observed true fibrinolysis in 1 case of myeloma* and in 1 probable case of disseminated lupus erythematosus

The connection between the globulin fractions responsible for positive eu cryo and macroglobulin tests cannot yet be definitely established although they certainly are closely related It is obvious that not all euglobulins are macroglobulins The simultaneous appearance of euglobulin and cryoglobulin in kala azar and in disseminated lupus erythematosus is quite common In one case of the latter disease it could be demonstrated that a considerable part of the serum proteins consisted of a high molecular globulin ($S_0 = 19$ to 20 S) It seems probable that in this case euglobulin macroglobulin and cryoglobulin were present in the same protein fraction On the other hand serums may contain large quantities of macroglobulin without a positive euglobulin or cryoglobulin reaction (Fig 8)

ANTICOMPLEMENTARY EFFECT OF GAMMA GLOBULIN

In 1917 Brahmachari (22) noticed an anticomplementary effect of kala azar serum and discussed its connection with hyperglobulinemia In 1937 Jersild (69) studied this effect and showed that so called auto inhibition is frequent in myeloma The same phenomenon has been observed in a number of other conditions with increased serum globulins such as lymphogranuloma inguinale liver cirrhosis and disseminated lupus erythematosus

In 1939 Jersild and Pedersen (70) studied the serum of a myeloma patient with a globulin content of 8 8 per cent The anticomplementary effect appeared at 56 C and was strongest at 58 C The results of ultracentrifugation were interpreted as showing the absence of Bence Jones protein and a markedly increased S 7 component

Of special interest is the investigation by Holmberg and Gronwall (66) of the serum globulin in a case of typical chronic arthritis without any signs of myeloma The serum had an anticomplementary effect When left standing in a closed vessel no precipitation set in even after 24 hours left in an open vessel rapid crystallization occurred at both 4 and 38 C This excludes the presence of cryoglobulin The precipitate was quite heavy (1 3 Gm /100 cc) A solution of the crystallized globulin gave a positive Wassermann reaction whereas *the serum remaining after precipitation was negative* in this respect Electrophoretic separation did not change the anticomplementary action of the pathologic protein

Davies *et al* (35) in a study of the anticomplementary activity of serum gamma globulin showed that gamma globulins prepared from

by Lerner and Watson (79) and Lehmann and Flemberg's second case suffered from chronic arthritis without signs of myeloma Leukemia of different types has also been observed in association with cryoglobulinemia Schwartz and Jäger (124) observed a remarkable case of se

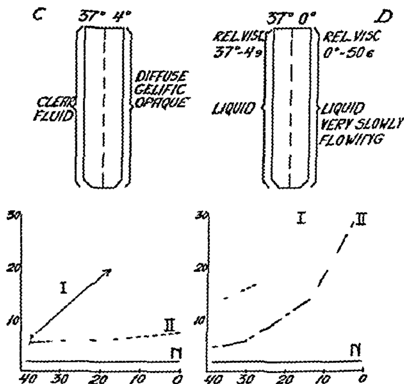


FIG 8 (cont)—C macroglobulinemia with total gelification as seen in 2 typical cases D extreme increase in viscosity at low temperature without gelification I typical case of macroglobulinemia II diagnosis not established (but not macroglobulinemia or myeloma) with cryoglobulin sometimes precipitating and an increase in S 20 component

vere cryoglobulinemic purpura in a patient with lymphatic leukemia Hansen and Faber (60) regarded their case as "aleukemic plasma cell leukemia" The difficulty of differential diagnosis in these various conditions makes it probable that plasmacytoma may be more commonly associated with cryoglobulinemia than we believe at present In a number of Swedish patients with myeloma whose serum proteins have been analyzed carefully the clinical picture of cold purpura with necroses was rarely seen I have never seen it in macroglobulinemia

gated by many workers Devine (39) noted that the amino acid composition of several Bence Jones proteins was different and conclud ed that there are different Bence Jones proteins Recently Dent and Rose (36) analyzed the amino acid pattern of several samples of Bence Jones proteins from different patients They found that none of these samples contained methionine

In view of the fact that Bence Jones protein appears in large quan tities in the urine it seems probable that its molecular weight is lower than that of the other serum proteins This assumption is corroborated by the fact that it is very difficult, if not impossible to demonstrate the presence of Bence Jones protein in blood serum. Early ultracen trifugal determinations by Svedberg and Sjogren (138) seemed to in dicate that the molecular weight of this protein fraction was only about 36 000 (sedimentation constant, 3 5 S) This would allow its passage through the glomerular membrane McFarlane (90) later examined Bence Jones protein from another patient and found a higher sedimen tation constant The isoelectric points of these two proteins differed Malmros and Blix (94) found a sedimentation constant of 3 6 S Often but not always it is possible to crystallize this protein fraction (68 91) The variations in the form of the crystals support the view that the Bence Jones proteins from different patients are not identical

Rundles *et al* (118) have studied the relation of abnormal serum components to Bence Jones protein in multiple myeloma Abnormal serum components examined in 14 different patients had sedimentation constants of $S_0 = 6.2$ to 6 8 S The diffusion rates varied between 3 1 and 5 0 (10 patients) and the majority of the calculated molecular weights fell within the limits of 140 000 to 160 000 with maximal varia tions from 120 000 to 200 000 The authors conclude that "the serum fractions in myeloma are homogenous abnormal proteins of high mo lecular weight Bence Jones proteins are of low molecular weight and can apparently be filtered by the glomeruli from the abnormal serum components

No reliable methods for the detection of small amounts of Bence Jones protein in the serum are available Hektoen and Welker (62) Robinson (115) and Moore *et al* ((98) isolated this protein from the urine and immunized rabbits with these preparations They produced an antiserum against the Bence Jones protein of a patient and used it to precipitate the Bence Jones protein present in the serum of the same patient The sedimentation constants of the Bence Jones protein from 4 cases were found to be 2 8 S 3 4 S 3 4 S and 3 4 S It was thus evi

normal serums may be markedly anticomplementary Inactivation at 56 C for 30 minutes strikingly reduced the effect in most but not in all cases Five different preparations of pure normal gamma globulin had equal anticomplementary effects per unit of protein Albumin neutralized the anticomplementary effect Purified Wassermann antibody has been found to be anticomplementary and migrates between beta and gamma globulin in the electric field It seems to be associated with both a light and heavy globulin component (S 7 and S 20) Olhagen (103) in a detailed study found that normal gamma globulin had an anticomplementary action and that anticomplementary gamma globulin was thermostable

These findings indicated that the anticomplementary effects of myeloma serum are not necessarily due to the presence of a pathologic protein component The anticomplementary action may well be the result of a pathologic increase of a normally occurring gamma globulin

In myeloma clumping of the red blood corpuscles may be so intensive that counting of the cells is impossible This phenomenon is also seen in serum with a high titer of cold agglutinins as happens in hemolytic conditions and after viral pneumonia Cold agglutinins have never been reported in multiple myeloma When cryoglobulin is present clumping of erythrocytes also occurs In both conditions clumping is prevented by performing the count at 37 C Cryoglobulin is observed as a precipitate in the serum on cooling In the counting chamber precipitates of cryoglobulin should not be confused with protein that has been precipitated by the mercury of Hayem s solution The erythrocytes are then clumped together on the precipitated protein After dilution with saline instead of Hayem s solution the erythrocytes can easily be counted

Lysis of blood clots deficient clot retraction and a bleeding tendency sometimes caused by a circulating anticoagulant (88) have been described in myeloma The important and interesting problem of amyloidosis in multiple myeloma is too complex to be treated briefly here Pohl (111) discusses this subject in detail

BENCE JONES PROTEIN

The first abnormal protein discovered in multiple myeloma was the urinary Bence Jones protein

The chemical composition of Bence Jones protein has been investi

Some authors have discussed the possibility that Bence Jones protein might occur in the serum in complex form of larger molecular size It could then be present in the serum even when it cannot be found in the urine So far no experimental proof for this assumption has been published

EFFECT OF TREATMENT OF MYELOMA ON SERUM PROTEINS

Loge and Rundles (85) treated myeloma with large doses of urethane (ethyl carbamate) In 2 cases the globulin value fell markedly (from 6 6 to 4 4 and from 5 5 to 3 6) in the third slightly (from 4 7 to 4 4) The albumin increased (from 3 4 to 5 1 from 2 5 to 4 4 from 3 8 to 4 3) The gamma globulin percentage fell in 1 case from 49 per cent to the normal value of 18 per cent and in another from 46 per cent to 24 per cent In the third case a globulin was present which the authors regarded as an M component (probably a beta globulin) This represented 45 per cent of the total protein before treatment and 33 per cent 3½ months afterward Definite signs of recalcification were found in 1 patient 6 months after the start of treatment There was no further progression of the destruction and the pains subsided The myeloma cells in the marrow diminished and the morphology changed remarkably No basophilic granulation in the cytoplasma was found such as is seen during treatment with stilbamidine

The first clinical successes with urethane treatment of myeloma were reported by Alwall (6) In 1 case in which skeletal pains were the chief complaint no change was observed on the administration of 3 to 4 Gm of urethane daily for 4 months The pains responded favorably to intravenous treatment with stilbamidine Another patient who suffered from myeloma and severe anemia was given urethane only and the treatment was continued indefinitely The anemia albuminuria hyperglobulinemia and increased sedimentation rate all improved considerably during the first 4 months of treatment Plasma cells disappeared from the marrow The condition of this patient remained rather favorable for 3 years a relapse then occurred which caused death after 1 year [personal communication from Dr Alwall]

Saltzmann and Borgstrom (118a) treated a patient with typical myeloma with 1 5 Gm of urethane thrice daily for 20 days This series was followed by several more courses of urethane administration After the first 10 days of treatment the nodules under the scalp became much smaller and after 20 days had disappeared and were replaced by depressions in the skull There was also a dramatic roentgenograph

dent that the molecular weights of these protein fractions were much lower than those of normal globulins with sedimentation constants of approximately 7 S

The dominant protein fraction in the serum in each case was isolated electrophoretically and then subjected to ultracentrifugation It was found to have sedimentation constants of 4 0 7 1 and 7 1 S One of the so called M components obviously had a very low sedimentation constant According to our experience in Upsala globulins with a low sedimentation constant are rarely found in whole serum Possibly denaturation had occurred during purification of the fraction

On the addition of Bence Jones protein to normal serum an extra peak in the electrophoretic diagram is found with a mobility corresponding to that of the added Bence Jones protein but different from the gamma globulins There were a few instances in which the mobility of the urinary Bence Jones protein was extremely slow

These data would seem to indicate that the molecular weights of the urinary Bence Jones protein must be much smaller than that of the pathologic gamma globulins of the serum Bence Jones protein cannot account for a large part of the serum globulin With the aid of a specific antiserum the Bence Jones protein present in the serum of 1 of these patients was found to be only 0 2 Gm per 100 cc Such small amounts obviously cannot be detected by electrophoresis or ultracentrifugation

The interpretation of some of these data is difficult because it would require electrophoretic isolation of the pathologic serum protein in a pure state Investigations of this kind with paper electrophoresis are in progress (75)

Janssen (68) found that his 4 patients with beta myeloma did not have Bence Jones protein in the urine whereas 50 per cent of his 23 patients with an increase in the gamma component did excrete Bence Jones protein The latter protein was isolated and added to the serum of the patient In 3 cases the urinary protein migrated with the velocity of a beta globulin in 3 others it behaved like a gamma globulin Thus in no circumstance should the abnormal protein in the urine be identified with the dominant serum protein fraction

It is true that Bence Jones protein is often found in normoproteinemic myeloma nevertheless many patients with myeloma with normal blood proteins excrete no Bence Jones protein In other series there are just as many such patients without proteinuria Thus the normal serum protein content cannot always be explained by a loss of abnormal protein via the urine

especially high In some instances the albumin is decreased and these two protein fractions often change in the opposite direction Bjørneboe (17) in his work on experimental hyperglobulinemia in rabbits has assumed that the hypoalbuminemia represents a compensatory reaction which is needed to conserve the colloid osmotic pressure of the blood at a normal level It seems more likely that in such cases the pathologic globulin fractions may have "a higher priority for the available amino acids than the albumin In the competition for the building stones the pathologic globulins apparently have a preferential position This theory would explain why the albumin is nearly always decreased in hyperglobulinemia and also why the formation of normal antibodies is impaired in these conditions (77)

The pathologic protein in lymphogranuloma inguinale belongs to the gamma fraction with a sedimentation constant of S 7 (153) In this disease the electrophoretic diagram shows a very broad gamma peak which differs completely from the narrow peak of the myeloma globulins The same broad peak is found in experimental immunization and in a number of other conditions such as liver cirrhosis and rheumatic" diseases

The gamma globulin fraction contains a large part of the different antibodies According to Sonck increased globulin in lymphogranuloma inguinale persists as long as the virus infection is active but becomes normal when the disease is healed The increase in gamma globulin is evidently caused by the virus infection Demonstration of a high titer of protecting antibodies against the virus in the gamma but not in the beta fraction would be strong proof of the specific antibody character of the increased gamma fraction It is interesting that the immunizing processes against a single virus can cause such a general increase in the bulk of the gamma globulin Blom (19) found in 1 case of this disease with hyperglobulinemia not only an anticomplementary factor to the Wassermann reaction but also a positive reaction to the test for heterophile antibodies Continuous immunization for many years against a strongly antigenic virus obviously may give rise to the formation of a number of different antibodies

A high globulin content usually accompanied by a low albumin content is often found in the serum of patients with liver cirrhosis It is a common belief that the low serum albumin in liver damage is a sign of impaired synthesis by the diseased liver cells It is also possible that the primary process consists of the formation of large amounts of globulin with a secondary lowering of the albumin production This

ic improvement The pains ceased almost completely the sedimentation rate came down from 70 to 8 mm in 1 hour and later to 3 mm A relapse occurred after 1 year but roentgenographs of the skull remained normal

Thorn (141) has reported 1 case of myeloma in which under influence of ACTH the serum globulin decreased from 10 2 to 4 8 Gm per 100 cc At the same time the plasma cells disappeared from the bone marrow Pearson seems to have noted favorable effects on the serum globulins but not on the plasma cells Dameshek has also mentioned that under the influence of ACTH the serum proteins in 2 patients became normal

Efforsoe (45) treated 6 cases of myeloma with ACTH In all instances a considerable decrease in the total serum protein was observed This may be explained by an increased plasma volume by increased break down of proteins or by decreased synthesis of proteins The excretion of Bence Jones protein diminished However the pathologic fractions in the blood failed to decrease and the number and cytologic characters of the plasma cells in the bone marrow remained unchanged The effect of the treatment was thus rather unsatisfactory The polyfractionation method of Effersoe demonstrated only a moderate decrease in the pathologic serum component

Engle and Barr have reported 3 cases of multiple myeloma treated with ACTH One patient had a spontaneously precipitable and crystallizable protein in the serum with severe Raynaud s syndrome Treatment produced no appreciable change in the plasma cells or in the amount of serum proteins In the discussion of this communication Bethell gave a short summary of his results with ACTH and cortisone in 8 cases There seemed to have been a marked influence on the plasma proteins in only 1 case Engle in the same discussion gave an account of 1 case in which Bence Jones protein became almost undetectable and serum globulin decreased markedly during prolonged treatment with ACTH

DISCUSSION

Abnormalities in protein metabolism form the central problem in the pathophysiology of multiple myeloma Among the other maladies with marked hyperglobulinemia lymphogranuloma inguinale is caused by one of the larger virus molecules it is a chronic disease but may be improved by sulfonamides As long as the virus is active the increase in serum globulins persists In such cases the gamma component is

especially high In some instances the albumin is decreased and these two protein fractions often change in the opposite direction Bjørneboe (17) in his work on experimental hyperglobulinemia in rabbits has assumed that the hypoalbuminemia represents a compensatory reaction which is needed to conserve the colloid osmotic pressure of the blood at a normal level It seems more likely that in such cases the pathologic globulin fractions may have "a higher priority for the available amino acids than the albumin In the competition for the building stones the pathologic globulins apparently have a preferential position This theory would explain why the albumin is nearly always decreased in hyperglobulinemia and also why the formation of normal antibodies is impaired in these conditions (77)

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explanation has already been discussed The globulin in portal cirrhosis is usually of the gamma type Ahrens *et al* (4) pointed out that biliary cirrhosis is characterized by an increase of the beta and not of the gamma globulin fraction This may be a clue to the obscure problem of the functional importance of the beta globulins It certainly indicates that liver damage of different etiology causes different patterns of the serum proteins These authors note that in this condition the serum albumin is less decreased than in other types of cirrhosis The increase in the beta component is closely correlated with a high content of serum lipids and may well be secondary to the derangement of lipid metabolism

Even if the lowered serum albumin in portal cirrhosis could be due to impaired synthesis by the liver cells the high gamma globulin content remains unexplained The serums of a large group of patients with liver damage of the chronic hepatitis type have recently been examined by Pedersen and the author [unpublished] In this group high gamma globulin was demonstrated with a corresponding increase in the S 7 component in the ultracentrifuge The albumin was usually low The gamma peak was of the same type as found in lymphopathia venereum We have ventured the hypothesis that a number of these cases of chronic liver disease with high gamma fraction are actually instances of a chronic virus infection This concept is in agreement with the present theories that acute viral hepatitis is a common cause of chronic cirrhosis It has recently been pointed out that liver cirrhosis may sometimes be treated successfully with the administration of aureomycin Since toxic substances produced by intestinal bacteria may damage the liver antisepsis of the intestinal tract with aureomycin could perhaps lead to improvement of the liver function The action of aureomycin on the virus of hepatitis has also to be considered The gamma fraction contains protective antibodies against the virus of acute hepatitis against the virus of measles and possibly against a number of other viral pathogens

Other chonic viral diseases are almost unknown and their influence on the serum proteins cannot be investigated Acute viral infections obviously have a marked influence on the serum proteins even if this is more qualitative than quantitative In this connection the therapeutic effect of measles on the course of nephrosis in children should be mentioned It has been observed that the severely deranged protein metabolism of the nephrosis patient is much improved after the virus infection For the diagnosis of infectious mononucleosis the

Paul Bunnell reaction i e the presence of heterophile antibodies is of practical importance It has also been shown that a positive reaction in thymol test is not only common in viral hepatitis but also in mononucleosis and measles This globulin reaction may well represent a response to *different* viral infections The lifelong immunity against a large number of acute viral diseases must be connected with antibody formation Production of antibodies is possibly stimulated by latent virus remaining in the organism after the acute phase of the disease has passed This has been well demonstrated by Burnet (26) in his important work on latent infection with herpes virus The presence of herpes virus in the body can as a rule be diagnosed only by demonstrating the presence of antibodies The virus is reactivated when the resistance of the host is lowered by an intercurrent disease such as pneumonia

High serum globulin is found in kala azar caused by a Leishmania that lives intracellularly e g in the spleen Granuloma inguinale is caused by a possibly related organism This organism lives in the lymph nodes and is also present in the form of intracellular Donovan bodies In the latter disease high globulin values have also been found (139) Cooper *et al* (30) demonstrated that in 1 patient with kala azar the serum albumin amounted to 2 6 Gm per 100 cc the globulin to 9 5 Gm per 100 cc with considerable increase of the gamma fraction Another case showed similar but less marked changes This gamma component resembled the gamma globulin found in chronic viral infections The globulin pattern reverts toward normal during successful treatment

Have all these different maladies certain characteristics in common which could help to explain their special tendency to form gamma globulins? Leishmaniae are microorganisms present as inclusion bodies in the interior of the cells Viruses also live in the interior of the cells It seems possible that the intimate spatial connection between host and parasite may account for their strong antigenic properties with marked influence on the protein forming systems of the invaded cells

In bacterial infections marked globulin increase is not found so commonly A small percentage of cases suffering from tuberculosis may have increased gamma globulin It is probable that amyloidosis arises chiefly in patients who have had long standing hyperglobulinemia Patients with subacute bacterial endocarditis and leprosy also often show a moderate degree of globulin increase and electrophoretic studies have shown increase in the gamma fraction

Similar findings obtained in a number of maladies of unknown origin are interesting Salvesen (119) first demonstrated that in sarcoidosis the serum globulins are much more frequently increased than in tuberculosis Pedersen and the author have been able to follow the changes of the serum proteins in a chronic case of sarcoidosis with involvement of the salivary glands and a chronic purpura hyperglobulinemica The globulin content remained high for at least 13 years It was caused by a marked increase in the S 7 gamma component of the virus type The hyperglobulinemia also militates against the hypothesis that sarcoidosis is a hyperergic response to a chronic infection with tuberculosis In the "rheumatic maladies or collagenoses" an increase in the gamma fraction is a common occurrence In the most severe form so-called disseminated lupus erythematosus high gamma globulin low albumin excess of anticomplementary factor high titer of different agglutinins and a positive reaction in Coomb s test are indications of disrupted protein metabolism Both in this disease and in periarteritis nodosa a high molecular cryoglobulin which precipitates on cooling is occasionally present Similar fractions are also found in kala azar Chronic arthritis may not show any peculiar disturbance of the quantitative protein pattern Qualitative changes are present and can be visualized by the agglutination of sensitized sheep erythrocytes In other cases excessive hyper gamma globulinemia may last for decades All of these changes support the concept of an hyperergic state i e one of hyperimmunization as the cause of hyperglobulinemia

A number of etiologically obscure cases of hyperglobulinemia with a broad gamma fraction designated as essential hyperglobulinemia, may thus actually be connected with antibody responses to benign viral infections or states of hyperergy of different origin

It is now generally accepted that the plasma cells in myeloma are the cause of the hyperglobulinemia In cases of quantitatively normoproteinemic myeloma it could be assumed that an unusually rapid turnover of some protein fractions exists so that they are broken down with the same speed as they are synthesized Experimental work with isotopic labeling of serum proteins in such cases may shed light on this problem Many authors seem to accept the neoplastic nature of myeloma cells The generalized occurrence the absence of primary tumors and of secondary metastases as well as the recently established influence of urethane and ACTH treatment upon these cells speak in favor of a systemic disease analogous to leukemia and against the more classic concepts of malignant neoplasia

In myeloma there is usually an increase either of the gamma or of the beta fraction Mixed cases where both fractions are increased are rare Our own observations indicate that even in the presence of one seemingly homogeneous electrophoretic component (gamma or beta fraction) on ultracentrifugation two pathologically increased components may be found (S 7 and S 11) Certain cases of myeloma seem to synthesize increased amounts of more than one globulin fraction The tendency to form these abnormal protein fractions is occasionally lowered by the administration of urethane or ACTH When this occurs the serum albumin often increases In myeloma an abnormal tendency toward the formation of large amounts of one or sometimes of several protein fractions exists The broad hyperergic (virus) gamma globulin peak in contrast to the narrow gamma peak in myeloma may indicate that not the whole gamma fraction is increased in myeloma but only one or a few members of this fraction

The question whether in myeloma completely abnormal proteins "paraproteins" or only an increased quantity of normal proteins are formed can hardly be answered on the basis of present knowledge The occurrence of proteins with a molecular weight that cannot be found in normal serums and the peculiarities of the Bence Jones protein speak in favor of an entirely abnormal protein component in these serums but other explanations remain possible

Stanley has found that certain plant viruses (tobacco mosaic) direct the protein synthesis of an infected plant toward the formation of virus protein The plant then contains increased amounts of protein which consist to a large extent of virus protein The same process seems to be found also in phage infected bacteria Certain analogies perhaps exist with genes which are also capable of autocatalytic actions and with the organizers studied by the experimental embryologists It does not seem improbable that one or possibly several "templates" for the synthesis of individual proteins may be modified by a virus like or genelike influence This would lead to an unlimited formation of pathologic products which would use up the available building stones and produce a secondary deficiency of normal body protein with resulting disease and death

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